Orthopaedics for the Newborn and Young Child

A Practical Clinical Guide

John F. Sarwark
Rebecca L. Carl
Editors

MOREMEDIA
Springer

Orthopaedics for the Newborn and Young Child

John F. Sarwark • Rebecca L. Carl
Editors

Orthopaedics for the Newborn and Young Child

A Practical Clinical Guide

Springer

Editors
John F. Sarwark
Feinberg School of Medicine
Northwestern University Feinberg School of Medicine
Chicago, IL, USA

Rebecca L. Carl
Feinberg School of Medicine
Northwestern University Feinberg School of Medicine
Chicago, IL, USA

ISBN 978-3-031-11135-8 ISBN 978-3-031-11136-5 (eBook)
https://doi.org/10.1007/978-3-031-11136-5

This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Preface

Infants and young toddlers experience unique orthopedic issues. This book focuses on those early musculoskeletal conditions that present in the first 1–2 years of life. When we developed the proposal for this text, we wanted to create a practical resource for pediatricians, family medicine doctors, neonatologists, residents in training, and licensed independent practitioners that would describe a range of common and rare conditions associated with their orthopedic findings in very young patients.

The introductory section of this book provides an overview of embryology and development to help clinicians understand the root of many congenital orthopedic conditions. We have also included a chapter on the musculoskeletal physical examination aimed at screening infants and young children for orthopedic conditions.

The next sections of the textbook focus on congenital orthopedic conditions and congenital syndromes with orthopedic manifestation. In later sections, this book addresses early musculoskeletal findings found with systemic diseases and neuromuscular disorders.

Each topic is presented in a concise chapter format designed for easy reference in the clinical setting.

We sincerely thank the authors for sharing their expertise in this publication. We express our appreciation and gratitude to Stephanie Frost and the editorial staff at Springer for their dedication and support in this endeavor.

Chicago, IL — John F. Sarwark
Chicago, IL — Rebecca L. Carl

Acknowledgments

We would like to dedicate this book to the parents, guardians, and other family members of our young patients and to the health professionals who care for them.

Contents

Contributors

Merritt E. Adams, MBBS Department of Orthopedic Surgery, Children's Hospital at Erlanger, UT College of Medicine Chattanooga, Chattanooga, TN, USA

Suzanne Amaro, APRN, MSN, FNP-C Department of Orthopaedic Surgery, Ann & Robert H. Lurie Children's Hospital, Chicago, IL, USA

Melanie Baskind, MD Department of Pediatrics, UCSF Benioff Children's Hospital, San Francisco, CA, USA

James T. Bennett, MD Department of Orthopaedic Surgery, Children's Hospital of Los Angeles, Los Angeles, CA, USA

Children's Surgical Specialty Group, Children's Hospital of the King's Daughters, Norfolk, VA, USA

Melissa A. Bent, MD Department of Orthopaedic Surgery, Children's Hospital of Los Angeles, Los Angeles, CA, USA

Michael D. Cabana, MD, MPH Department of Pediatrics, Albert Einstein College of Medicine, Physician-in-Chief, The Children's Hospital at Montefiore (CHAM), Bronx, NY, USA

Lisa A. Cao, MD Department of Orthopaedic Surgery, LAC+USC Medical Center, Los Angeles, CA, USA

Rebecca L. Carl, MD, MSCI Feinberg School of Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

Sarah Carlson, ATC/OTC, BS Department of Orthopaedic Surgery, Ann and Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA

Priya Chandan, MD, MPH Division of Physical Medicine & Rehabilitation, University of Louisville, Louisville, KY, USA

Sheila Chandran, MD Department of Orthopedics, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA

Miranda De Loof, MSN, APRN, FNP-BC Division of Orthopaedic Surgery and Sports Medicine, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA

Linda A. DiMeglio, MD, MPH Department of Pediatrics, Indiana University School of Medicine, Riley Hospital for Children, Indianapolis, IN, USA

Mary E. Dubon, MD Department of Pediatric Rehabilitation, Spaulding Rehabilitation Hospital, Charlestown, MA, USA

Department of Physical Medicine & Rehabilitation, Harvard Medical School, Boston, MA, USA

Department of Orthopedics Surgery and Division of Sports Medicine, Boston Children's Hospital, Boston, MA, USA

Bensen B. Fan, MD Department of Orthopaedic Surgery, Children's Hospital of Los Angeles, Los Angeles, CA, USA

Orlando Health Arnold Palmer Hospital for Children Center for Orthopaedics, Orlando, FL, USA

Craig J. Finlayson, MD Division of Orthopaedics and Sports Medicine, Ann and Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA

Eric B. Fuller, BS, MD Department of Orthopaedic Surgery, Ann & Robert H. Lurie Children's Hospital, Chicago, IL, USA

Srirupa Hari Gopal, MD Department of Pediatrics, Erlanger Hospital, University of Tennessee College of Medicine at Chattanooga, Chattanooga, TN, USA

John J. Grayhack, MD, MS Baylor College of Medicine, Houston, TX, USA

James D. Hammond II, MD Department of Pediatrics, Ann and Robert H. Lurie Children's Hospital of Chicago, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

Neal Huang, BS, MD Department of Orthopedic Surgery, University of Tennessee College of Medicine Chattanooga, Chattanooga, TN, USA

Joseph A. Janicki, MD Ann and Robert Lurie Children's Hospital of Chicago, Chicago, IL, USA

Angielyn San Juan, DO Department of Orthopaedics, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA

Northshore University Health System, Skokie, IL, USA

Annemarie Fox Kelly, MD Department of Pediatrics, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA

Erik C. B. King, MD, MS Department of Orthopaedic Surgery, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA

Jill E. Larson, MD Ann & Robert H. Lurie Children's Hospital, Chicago, IL, USA

David K. Lyons, DO Department of Pediatric Orthopaedics, Ann and Robert Lurie Children's Hospital of Chicago, Chicago, IL, USA

Kyle L. MacQuarrie, MD, PhD Department of Pediatrics, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA

Sina Malekian, BS Department of Orthopaedic Surgery, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA

Ayesha Maqsood, MD, MBA Department of Surgery, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA

Elizabeth N. Martin, MD, MPH, MHS Department of Pediatric Rehabilitation Medicine, Mary Bridge Children's Hospital, Tacoma, WA, USA

Kristine Santos Martin, MSN, APRN, CPNP Division of Orthopaedic Surgery and Sports Medicine, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA

Alison Murray, MD Department of Pediatrics, Ann & Robert H Lurie Children's Hospital of Chicago, Chicago, IL, USA

Muhammad Y. Mutawakkil, MD Department of Orthopaedic Surgery, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

Richard W. Nicolay III, MD Department of Orthopedic Surgery, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA

Kathryn Oelsner, MD Department of Pediatrics, University of Tennessee-Chattanooga, Erlanger Hospital, Chattanooga, TN, USA

Andrea Paulson, MD, MPH Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, OH, USA

Parker D. Plant, DO Department of Pediatrics, Erlanger Hospital, Chattanooga, TN, USA

Mia M. Qin, MD Department of Orthopedic Surgery, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA

Robert S. Quigley, MD Department of Orthopedic Surgery, University of Tennessee College of Medicine Chattanooga, Chattanooga, TN, USA

Deirdre De Ranieri, MD, RhMSUS Department of Pediatric Rheumatology, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA

Michelle L. Sagan, MD Division of Pediatric Orthopaedic Surgery and Sports Medicine, Ann and Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA

John F. Sarwark, MD Feinberg School of Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

Diane Dudas Sheehan, ND, APRN, FNP-BC Division of Orthopaedic Surgery and Sports Medicine, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA

Department of Physical Medicine and Rehabilitation, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

Haley E. Smith, MD Department of Orthopedics, Northwestern University, Chicago, IL, USA

Ognjen Stevanovic, MD, PharmD Department of Orthopaedic Surgery, Northwestern University, Chicago, IL, USA

Natalie C. Stork, MD Department of Orthopaedic Surgery and Musculoskeletal Science, Children's Mercy Hospital Kansas City, Kansas City, MO, USA

Departments of Orthopaedic Surgery and Pediatrics, University of Missouri-Kansas City School of Medicine, Kansas City, MO, USA

Vineeta T. Swaroop, MD Department of Orthopaedic Surgery, Ann & Robert H Lurie Children's Hospital of Chicago, Chicago, IL, USA

Peter R. Swiatek, BA, MD Department of Orthopaedic Surgery, Northwestern Memorial Hospital, Chicago, IL, USA

Meghan K. Urban, MD Department of Physical Medicine and Rehabilitation, McGaw Medical Center of Northwestern Hospital, Chicago, IL, USA

Ehab H. Yasin, DO Department of Physical Medicine and Rehabilitation, Rush University Medical Center, Chicago, IL, USA

Alicia C. Zolkoske, MD Department of Orthopedic Surgery, Children's Hospital of Wisconsin/Medical College of Wisconsin, Milwaukee, WI, USA

Part I
Overview

Chapter 1
Essentials of Embryology for the Musculoskeletal System

James D. Hammond II

The Embryonic Period

Musculoskeletal development begins with a single cell known as a zygote. This event marks the beginning of a series of changes starting with the **embryonic stage of human development (weeks 0–8)**, setting the stage for the complex series of events that culminates with the development of a living human being. The newly created zygote is capable of differentiating into all of the cells in the human body, the starting point in the development of the musculoskeletal system. Within as few as 30 h after fertilization, the totipotent zygote undergoes multiple mitotic divisions in a process known as cleavage, the end result of this process is a rapid increase in the number of cells (**blastomeres**) all contributing to the formation of the spherical **morula** (embryologic structure composed of 12–32 blastomeres). This mass of cells will then enter into the uterus to become the blastocyst and ultimately implants itself into the uterine epithelium 6 days after conception. By the end of the first week after fertilization, the blastocyst, consisting of the **embryoblast**, **trophoblast,** and **blastocystic cavity**, has begun to implant into the endometrium and start the process of differentiation into the more complex future embryo.

Implantation of the blastocyst is completed by the end of the second week after fertilization. Once implanted, the embryoblast begins to differentiate into the **bilaminar embryonic disc**, a two-layer structure made up of the **hypoblast** and **epiblast**. As we will see later (Fig. 1.2), these two cellular layers are capable of further differentiation and eventually contribute cells to the entire human body. The process by which the bilaminar disc begins to differentiate is known as gastrulation and begins during the third week of development. Following gastrulation, the resulting trilaminar disc is made up of the **embryonic ectoderm, endoderm, and**

J. D. Hammond II (✉)
Department of Pediatrics, Ann and Robert H. Lurie Children's Hospital of Chicago, Northwestern University Feinberg School of Medicine, Chicago, IL, USA
e-mail: jhammond@luriechildrens.org

J. F. Sarwark, R. L. Carl (eds.), *Orthopaedics for the Newborn and Young Child*,
https://doi.org/10.1007/978-3-031-11136-5_1

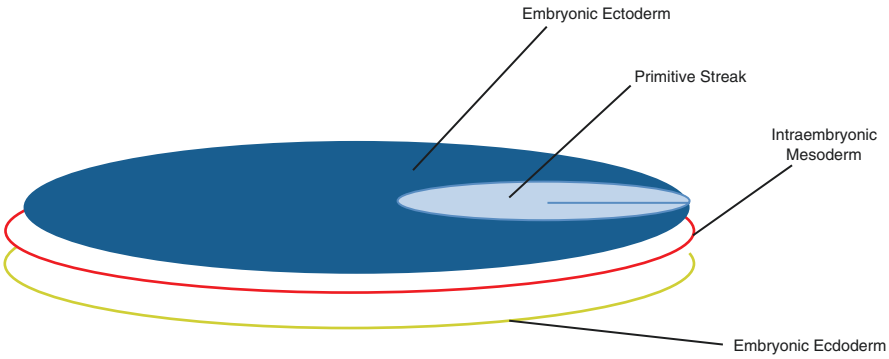


Fig. 1.1 Trilaminar disc composed of ectoderm, mesoderm, and endoderm

intraembryonic mesoderm (Fig. 1.1), the latter being the key contributor of the future musculoskeletal system.

The extent to which the trilaminar disc contributes to the developing embryo can be seen below:

Embryonic endoderm: Epithelial linings of respiratory and GI tracts and endocrine glandular cells.
Embryonic ectoderm: Nervous system tissues, epidermis, eyes, parts of the inner ear, neural crest cells and their derivatives including connective tissues of the head.
Embryonic mesoderm: All skeletal muscles, all connective tissues (cartilage, bones, tendons, ligaments) except for that of neural crest origin in the head, skin, and blood, lining of blood vessels, serosal linings, excretory glands, most of the reproductive system and cardiovascular system.

Gastrulation marks the beginning of morphogenesis, the process through which the embryo develops its human-like form. By the end of morphogenesis, the embryo has distinct polarity with a noticeably more human shape. The process starts in the third week of life following formation of the trilaminar disc when the **primitive streak** forms on the dorsocaudal surface of the epiblast of the disc. Cells are added to the end of this streak as it extends cranially, terminating eventually with the formation of the **primitive node** at the cranial most end of the streak. The **primitive groove** forms in the floor of the primitive streak from epiblastic cells destined to eventually become embryonic connective tissue (mesenchyme). Formation of the primitive groove establishes the craniocaudal axis of the embryo, which now has an appreciable left and right side with dorsal and ventral surfaces. By the end of morphogenesis, the embryo has a curve-like appearance with appreciable head and tail folds.

The epiblastic cells within the primitive streak contribute cells to embryonic connective tissue known as the **mesenchyme,** the mesenchymal cells eventually form most of our body's connective tissues after differentiating into the **mesoblast** (undifferentiated mesoderm) eventually forming the embryonic mesoderm (Fig. 1.2).

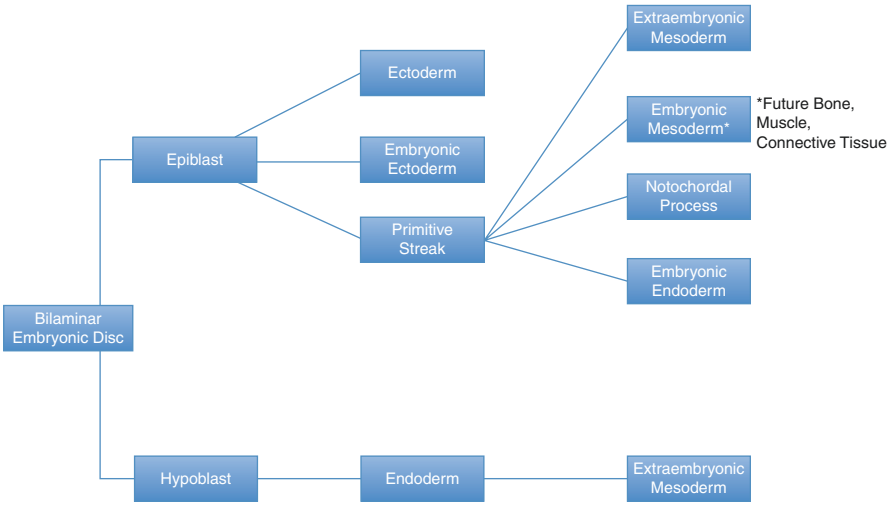


Fig. 1.2 Origin of embryonic tissues

Parts of the primitive streak and epiblast also become embryonic endoderm, and the remainder of undifferentiated cells forms the embryonic ectoderm. Following gastrulation, the primitive streak disappears into the sacrococcygeal region of the embryo. Failure of the primitive streak to regress can cause sacrococcygeal teratomas, a germ cell tumor that is also the most common tumor in newborns.

Around 17 days of life, the notochordal process forms from mesenchymal cells that travel through the primitive streak into the mesoderm. It grows cranially and laterally, expanding between layers of the endoderm and ectoderm until it reaches the ends of the embryonic disc at the oropharyngeal membrane cranially and cloacal membrane caudally. The notochordal process eventually forms a rod-like structure extending from the oropharyngeal membrane to the primitive node called the notochord, a structure that is vital to the future development of the embryo. The notochord adds structure to the embryo, but most importantly acts as a primary signaler driving development of the axial musculoskeletal structures (vertebral column, trunk muscles) before degenerating and becoming the nucleus pulposus of the intervertebral discs. Persistence of the notochord results in chordomas, benign tumors that typically form at the skull base and can invade locally and become malignant.

Before degeneration, the notochord induces the overlying ectoderm to differentiate into the neural plate, which becomes the CNS. Around day 18 of life, the neural plate begins to fold up on itself and the neural groove forms, flanked on either side by the neural folds which fuse by the end of the third week into the neural tube, the primordium of spinal cord and brain. As the neural tube develops, few neuroectodermal cells that transition from epithelial to mesenchymal cells are known as the neural crest cells. These cells migrate to the left and right dorsolateral aspects of the neural tube and become spinal ganglia and ganglia of the ANS. Some of them will go on to become sensory ganglia and a few will become ganglia for specific parts of

cranial nerves V, VII, IX, and X. It should be no surprise that problems with neurulation in the third-fourth weeks of life may lead to birth defects of the brain and spinal cord and are one of the most common congenital anomalies in newborns. Meroencephaly (absence of brain), more commonly called anencephaly, can also occur and is the most severe neural tube defect encountered in newborns.

The primitive node also contributes the cells that form the paraxial mesoderm, thick, columnar cells close to the primitive node continuous laterally with the intermediate mesoderm. Near the end of the third week of development, the paraxial mesoderm differentiates into cuboidal pairs of cells called somites (about day 20). These pairs extend craniocaudally along each side of the developing neural tube. By the end of the fifth week of development, 42–44 pairs of mesodermal somites are present, causing swellings along the neural tube, which eventually contribute to most of the axial and appendicular skeleton, its musculature and the overlying dermis. Each somite pair is initially patterned into the same ventral and dorsal components—then sclerotome and dermomyotome (future dermatome and myotome). The location of the somites along the neural tube is important for proper innervation of the musculoskeletal system, and Hox genes that control the future development of the axial skeleton regulate the somite patterning seen below (Fig. 1.3).

The fourth through eighth weeks of development mark the end of the embryonic period of development and are characterized by further development of the embryo into a recognizable human being containing the beginnings of all of the major organ systems. Because most essential internal and external structures are formed in this time frame, it is no surprise that the developing human is particularly susceptible to influences by genetic and environmental factors. Most major birth defects occur in this stage of development either due to chromosomal/DNA defects or the external influence of **teratogens** (agents that cause malformations). These major changes in

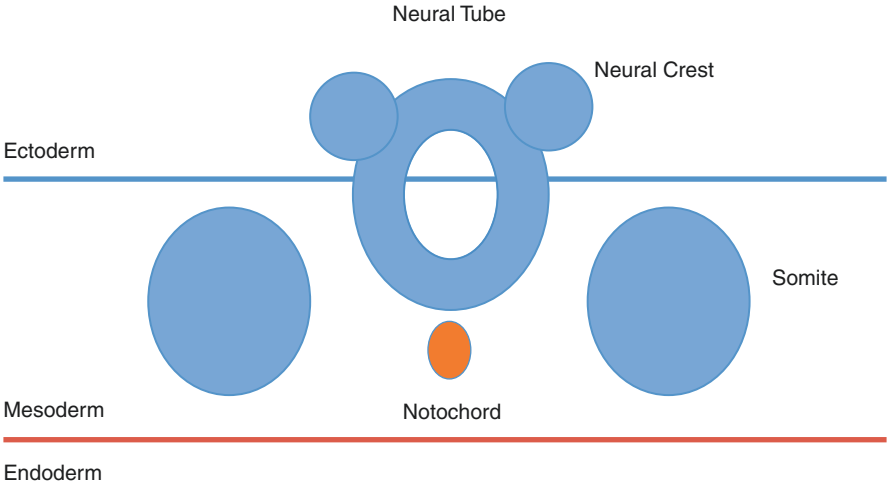


Fig. 1.3 Somite patterning along the neural tube

shape begin in the fourth week of development, as the somites located ventrolateral to the neural tube begin to further differentiate. By day 26, the upper limb buds have formed as swellings on the ventrolateral surface of the embryo, followed by the lower limb buds by the end of the fourth week. Folding of the embryo into a cylindrical shape also begins in the fourth week with the formation of head and tail folds in the median plane, and then subsequently, the formation of the lateral folds in the horizontal plane. By the sixth week, the upper limb buds have begun to differentiate with the development of elbows, the hand plate, and digital rays (primordia of future fingers). The lower limbs lag behind development of the upper limbs typically by 4–6 days. Noticeable changes occur to the limbs in the seventh week as clear digits form in the hand plates, and the process of ossification in the upper limbs has begun. The limbs continue to differentiate over several days and by the end of the eighth week, the embryo has a distinctly human appearance with purposeful movement of both upper and lower extremities.

The Fetal Period (8 Weeks-Birth)

The fetal period occurs from weeks nine through birth and is characterized by further differentiation and growth of the embryo into a human capable of living and breathing on its own. The limbs continue to develop and by the end of 12 weeks, the upper limbs have achieved their final relative length, and primary ossification centers have appeared in the long bones and skull. Limb movements are coordinated by the start of the 15th week, which can be both felt by mother as well as seen on ultrasound examination. Such marked growth and development as that which occurs in the fetal period require substantial nutrients, and several factors contribute to abnormal growth during this stage of development. Infants born preterm and underweight due to shortened gestational periods must be distinguished from low birth weight infants due to external causes. Factors that affect growth over the length of a pregnancy (hypertension, multiple gestation, smoking, alcohol consumption, infection, placental vascular insufficiency) lead to intrauterine growth restriction (IUGR) or small for gestational age (SGA) newborns that are typically symmetric in their relative small size (weight, body length, head circumference are equally affected). The two different conditions are distinct from each other in that IUGR infants suffer from a reduction in growth potential, and SGA infants are defined as infants with a birth weight < 2 STD below the mean. The terms can be confusing but are important to properly define when gathering historical information on a newborn.

Development of the Skeletal System

Development of the skeletal system occurs starting in the third week and continues until the growth plates close at around 25 years of age. Around 21 days of life, blocks of mesoderm known as **somites** begin to form on the dorsolateral surface of the embryo. These **primordial structures** are essential to the future development of the muscles and bones of trunk, as well as both the upper and lower extremities. Each somite pair will further differentiate into two parts known as the **sclerotome** (primordial vertebrae and ribs) and the **dermomyotome** (primordial muscles and skin).

In the fourth week of development, the sclerotome cells arrange themselves into embryonic mesenchyme. This matrix of connective tissue has the capability to form bones in a process that is regulated by a variety of genetic and environmental factors. First, mesenchymal cells condense and then are acted upon by specific genetic pathways to eventually form bones by both intramembranous and endochondral bone formation. BMP-5 and BMP-7 as well as TGF-B have been implicated in the process of chondrogenesis and bone modeling. Wnt signaling pathways are also involved in the formation of chondrocytes and osteoblasts.

The process of bone development first starts with the formation of cartilaginous models and then proceeds either by membranous or endochondral ossification. **Membranous osteogenesis** occurs in most flat bones, whereas the long bones of the extremities are formed as cartilage derived from the mesenchyme is later ossified **(endochondral osteogenesis).** Cartilage forms from embryonic mesenchyme in the fifth week as mesenchyme differentiates into a chondrification center. Each center consists of condensations of mesenchymal cells that have been acted on by signaling molecules to differentiate into chondroblasts, whose main responsibility is to secrete collagen fibrils and lay down extracellular matrix (ECM). The type of ECM secreted by the chondroblasts will ultimately determine the type of collagen formed, either forming the **hyaline cartilage** of joints, **fibrocartilage** of the intervertebral discs, or **elastic cartilage** of the ears.

Fetal bones arise from either mesenchyme directly or via ossification of the cartilage formed above. Like cartilage, bones are a connective tissue that also contains an ECM matrix embedded with cells acting via signaling molecules to coordinate differentiation and growth. Membranous ossification occurs in mesenchyme contained within membranous sheaths. It begins with condensation of the mesenchyme and formation of osteoblasts (bone-building cells) which deposit osteoid. As calcium and phosphate are deposited into the unmineralized bone matrix, the tissue is organized into bone with the help of osteocytes (bone-remodeling cells differentiated from osteoblasts). As osteoblasts at the periphery of the bone continue to lay down lamellae of bone around blood vessels within the matrix, osteoclasts actively resorb one creating the spongy areas of flat bones containing mesenchyme that has differentiated into the hematopoietic bone marrow.

Endochondral ossification, also known as cartilaginous bone growth, occurs within cartilage models formed beginning early in the fourth week of development from mesenchymal cells. The most classic example of endochondral ossification occurs in the long bones, where primary ossification centers arise in the diaphysis (shaft-like area of long bone located between the two ends). Here, chondrocytes hypertrophy, ECM calcifies, and the cells undergo apoptosis. Bone is simultaneously added underneath the perichondrium surrounding the diaphysis, which eventually becomes the periosteum. This thin layer of newly formed bone is invaded by blood vessels that assist in cellular breakdown within the ossification center. Osteoblasts are carried into the cartilaginous model to carry out their bone-building fates or in some cases differentiating into bone marrow cells. The process continues outwards towards the end of the bones to the epiphysis. Remodeling by osteoblasts and osteoclasts then occurs similarly to the process that occurs in membranous ossification.

Long bones are formed when new bone is added via endochondral ossification at specific regions of bone called **diaphyseal-epiphyseal junctions,** more commonly known as **growth plates.** In this region of the long bone, chondrocytes are actively proliferating and contributing to ossification when acted upon by osteoblasts and osteoclasts. As the cells migrate closer to the epiphysis, they begin to hypertrophy in preparation for programed cell death that awaits them. Calcification of the surrounding matrix occurs and slowly, bone is added on by osteoblasts that migrate into the bone through the vessels of the marrow. The bone grows in diameter when bone is deposited at the periosteum while internal medullary bone is simultaneously actively resorbed. This process is highly dependent on calcium and phosphorous balance in the mother, fetus, and the growing infant. It is for this reason that Vitamin D deficiency can lead to a condition known as rickets. Vitamin D assists with calcium absorption by the intestines. When it is deficient, the resulting hypocalcemia and hypophosphatemia disrupt the ossification of the epiphyseal cartilage plates, causing shortened limbs with characteristic bowing. It can also affect other irregular bones in the skull/cranium causing delayed fontanel closure. This process of ossification starts to occur near the end of the embryonic period around 55–56 days after fertilization.

At birth, the diaphyses of most long bones are ossified while the epiphyses are still cartilaginous. A few years after birth, secondary ossification centers form and the same process that occurs in primary centers occurs there, with the epiphyseal cartilage plate (growth plate) remaining as the sole source of chondrocytes available for lengthening of the bone. Irregular bones such as few found in the cranium also develop via endochondral ossification by a similar process, beginning centrally and spreading outwards to the periphery of the bone. Because there is a known pattern of development, bone age can be used as a fair index for maturation by examining the epiphyseal-diaphyseal junctions in certain bones.

Development of Axial Skeleton

The **axial skeleton** is the vertebral column, ribs, sternum, and cranium, and develops starting in the fourth week. The future vertebral column is derived from densely packed cells of the sclerotome formed from somites surrounding the notochord in the 4-week embryo. Patterning of the axial skeleton is regulated by Hox and Pax genes, similarly to patterning of the appendicular skeleton as we will later learn.

These cells migrate cranially away from the myotome to form intervertebral discs, and the notochord eventually becomes the nucleus pulposus. The more loosely packed cells of an associated sclerotome, located caudally, eventually arrange to form the centrum, the primordium of the vertebral body. Other mesenchymal cells surrounding the neural tube form the primordium of vertebral arch. Concurrently, the mesenchymal cells in the body wall form costal processes, which will ultimately become the ribs. The vertebral bodies begin ossification in the sixth week via three ossification centers in the centrum and each vertebral arch. Cartilaginous tissue supports the entire vertebral structure until ossification is complete. The vertebral arches fuse by 3–5 years of age. Following puberty, five secondary ossification centers can be found within each vertebral unit which all fuse by 25 years of age. VACTERL (Vertebral, Anal, Cardiac, Tracheal, Esophageal, Renal, Limb) and CHARGE (Coloboma, heart defects) are associated with Notch pathway genes responsible for the signaling involved in vertebral patterning.

Development of the Appendicular Skeleton

Appendicular growth trails slightly behind development of the axial skeleton beginning in the fifth week of life via Hox signaling pathways. The appendicular skeleton is the limb bones, the pelvic girdle, and the pectoral girdles arising from mesenchymal condensations starting in the limb buds. These mesenchymal bone models began to undergo chondrification into cartilaginous bone models in the sixth week of life with the upper limbs developing slightly before the lower limbs. Growth of the appendicular skeleton proceeds via endochondral ossification described above, and by 12 weeks of age all the primary ossification centers of the limbs have been formed. The clavicles begin the process of ossification first, followed by the femurs.

Common Congenital Disorders of Skeletal System

Common disorders of the musculoskeletal system can be grouped into either malformations, disruptions, deformations, or dysplasias. **Malformations** are a morphological defect in an organ resulting from an abnormal developmental process due to either intrinsic insults or a combination of intrinsic and extrinsic factors. **Disruptions**

are a defect in an organ due to interference of the developmental process via an extrinsic factor which occur when an organ is influenced by a teratogen. **Deformation**s occur as a result of external forces acting on an organ which occur in amniotic band syndrome or oligohydramnios. **Dysplasias** are a result of abnormal tissue formation. These different types of developmental defects can be seen as a combination of defects all related to a single factor when found in **sequences** or seen in **syndromes** when they are related but no single factor can be identified. Common problems with the musculoskeletal system often involve limb abnormalities, which we will learn about shortly, but birth defects can also be isolated to the skeletal system. Thus, for this section, we will mostly focus on disorders of the axial skeleton, which due to its close relation to the neural tube often involves nervous system disorders as well.

Klippel-Feil syndrome, or **brevicollis**, is a syndrome that involves abnormalities in vertebral bodies as well as the brainstem and cerebellum. Individuals with this syndrome often have a shortened neck due to fusion of the vertebral bodies, a low hairline, and restricted neck movement. Newborns with this condition can suffer from scoliosis and urinary tract disorders. Another relatively common birth defect involving the axial skeleton, though technically a defect in the nervous system, is **spina bifida** which can have secondary effects on the musculoskeletal system and thus lies within the scope of this chapter. It occurs when the cartilaginous neural arch fails to fuse properly. Its incidence is from 0.04 to 0.15%, and girls are more commonly affected than boys. The disease lies on a spectrum of neural tube defects and the management depends on the severity at presentation. The neural tube defects are commonly described by the extent of spinal cord exposure. In **spina bifida occulta,** there are usually no symptoms, with tufts of hair or overlying dimples being the only outward findings of disease. Whereas in **spina bifida cystica**, there is an overlying cyst found in the sacral region most commonly, but the defect can theoretically be located anywhere along the spine. When the cyst contains CSF and meninges, it is known as a **meningocele**. If the spinal cord is also found within the cyst, it is known as a **myelomeningocele**. These lesions can now be intrauterinely repaired at major academic institutions by neurosurgeons, then subsequently managed by a large group of medical and surgical providers. Another commonly encountered abnormality of the spinal cord is **rachischisis,** which refers to a **spinal dysraphism** in which the neural folds fail to fuse due to faulty induction from the notochord or teratogens. This disease also lies on a spectrum with varying level of neurologic compromise.

Cranial birth defects can also be seen in a number of congenital syndromes and genetic defects. They can range from incompatible with life to clinically insignificant. **Acrani**a occurs when there is partial or complete absence of the neurocranium. Vertebral column defects are commonly comorbid with isolated acrania, as well as **acrania with meroencephaly** (partial absence of brain), a more severe form, which is incompatible with life. These defects result from failure of the neural tube to close during the fourth week preventing the neurocranium from forming.

Craniosynostosis is a more commonly encountered anomaly of the cranium caused by premature fusion of the cranial sutures. Males are more commonly

affected and other skeletal anomalies are commonly seen. Craniosynostosis is classified by which suture is affected. In **scaphocephaly**, the most common type, the sagittal suture closes early and the resulting cranium is long, narrow and wedge-shaped. **Brachycephaly** is premature closure of the coronal suture and results in a high, cone-shaped head. **Plagiocephaly** occurs when only one coronal suture closes, resulting in a crooked, twisted cranium. Finally, trigonocephaly occurs with premature closure of the frontal suture. Craniosynostosis can cause restriction of growth of the head which subsequently restricts brain development and growth so early identification and correction are important. It is also important to distinguish craniosynostosis from isolated microcephaly, which is not caused by premature closure of the sutures but instead the failure of the CNS to develop. Infants with microcephaly generally suffer from intellectually disability due to abnormal brain growth, whereas infants with craniosynostosis who are appropriately treated have normal intelligence.

The commonly encountered congenital defects of the axial skeletal system involve the formation of extra bones or agenesis of other bones. **Accessory ribs** can be seen when there is abnormal development of the costal processes of cervical or lumbar vertebra. Lumbar ribs are the most common and are typically asymptomatic, seen as incidental findings on chest radiographs. Cervical ribs occur in 0.5–1% of the population and can lead to brachioplexus/subclavian artery compression and neurovascular symptoms [1]. **Fused ribs** are also seen when multiple ribs arise from the same vertebra. These are also usually asymptomatic when they are seen as isolated defects but can cause issues when they occur with other defects. Comorbid to fused ribs are **hemivertebra**, caused when one of the chondrification centers never appears resulting in failure of half of the vertebra to form. Hemivertebra are the most common cause of congenital scoliosis making them clinically significant in some cases. **Cleidodysostosis** is another malformation sometimes encountered and is the absence of all or part of the clavicle. This malformation is typically bilateral, the shoulders are drawn forward to meet under the chin, and is commonly associated with skull defects.

Other generalized skeletal malformations commonly encountered are **achondroplasia** and **thanatophoric dysplasia**. Achondroplasia is the most common cause of dwarfism, occurring in 1:15,000 births [2]. In this disorder, the limbs are shorted and become bowed secondary to disruption in endochondral ossification at the epiphyseal plates of the long bones during fetal life. The trunk is typically also involved and shortened, with the head appearing large with a flat nasal bridge. It is inherited in an autosomal dominant fashion with 80% of cases coming from new point mutations in the FGFR3 gene. This causes increase in the normal inhibiting effect of endochondral ossification in the chondrocyte proliferation zone. The resulting bones are thus shortened. Thanatophoric dysplasia is another disorder involving the FGFR3 gene, however, it is always lethal with most infants dying within minutes due to respiratory failure. It occurs once in 20,000 births and is the most common, lethal, skeletal dysplasia.

The Muscle System

The skeletal muscles that comprise the majority of limb and axial muscles develop from myogenic precursor cells through a process known as **epitheliomesenchymal transformation**, regulated by the MyoD gene family. As you may remember, pairs of somites form during week 5 in a process known as segmentation resulting in 40–44 pairs eventually contributing to bones and muscles. The sclerotome forms on its ventromedial portion and migrates to the notochord where it gives rise to the fibroblasts, chondroblasts, and osteoblasts we previously encountered. Somites in the ventral area form dermomyotomes comprised of a dermatome and myotome that ultimately differentiate into myogenic precursor cells and epithelial cells. Mesenchymal cells are acted upon by MyoD genes and begin myogenesis. During this process, their nuclei and cell bodies elongate and eventually fuse to form elongated, multinucleated structures known as myotubes. **Myotubes** and **myoblasts** continue to form as muscles grow along with the fetus.

After fusion of the myoblasts, **myofilaments** begin to develop within the myotubes and the characteristic **myofibrils** also form. Finally, the myotubules are invested in a sheath that eventually is acted on by fibroblasts, producing the endomysium, perimysium, and epimysium layers of the fibrous muscle sheath. This entire process occurs mostly before birth and is completed by the end of year one of life. Any further increases in muscle size are due to an increase in muscle diameter as more myofilaments are created.

As previously mentioned, the process of muscle development begins when the myotome aspect of each somite divides into a dorsal epaxial and ventral hypaxial division. These divisions are important in discussing the innervation of skeletal muscles in the body. The dorsal-lying epaxial division is supplied by the dorsal primary ramus from the developing spinal nerves and the hypaxial by the ventral primary ramus. These divisions then further supply the mesenchymal tissue that ultimately becomes the myoblasts. Myoblasts from the epaxial divisions go on to form the extensor muscles of the neck and vertebral column. Myoblasts from the hypaxial divisions of the cervical myotomes form the scalene, prevertebral, geniohyoid, and infrahyoid muscles. The thoracic myotomes eventually contribute to the formation of the lateral and ventral flexor muscles of the vertebral column, and the lumbar myotomes form the quadratus lumborum muscles.

The musculature of the limbs develops alongside the bones that support them. Myoblasts concentrate on flexor and extensor surfaces of the developing bones after undergoing epitheliomesenchymal transformation in the ventral part of the dermomyotome. Muscles of branchial arch origin, ocular muscles, and tongue muscles are outside of the scope of this chapter, as are muscles of the heart and the smooth muscle of the gut; however, they too form from mesenchymal origin in a similar pattern.

Common Disorders of Muscle Development

Congenital malformations of muscle may be caused by failure of the muscle to develop or a pathologic process affecting the muscle/nerve unit during embryonic development. **Complete absence of a muscle** is more common than typically recognized, with the most common muscles affected being the palmaris longus, trapezius, serratus anterior, quadratus femoris, and the sternocostal head of the pectoralis major. The abnormality can be bilateral or unilateral in nature and usually causes no significant clinical signs/symptoms when seen as isolated findings. Absence of the pectoralis major muscle can be associated with syndactyly, or as part of **Poland Syndrome** (absence of the pectoralis major and minor muscles, ipsilateral hypoplasia of the breast, and agenesis of ribs). When muscular defects of vital organs such as **congenital absence of the diaphragm** occur, patients can have clinical symptoms. In this defect, patients will have difficulty breathing and can get recurrent infections. In defects involving **absence of abdominal wall muscles**, you can also see additional gastrointestinal or urinary tract abnormalities such as exstrophy of the bladder. In **prune belly syndrome**, there is a complete or partial absence of the abdominal muscles due to accumulation of ascites fluid in the abdomen in utero. Males can have comorbid cryptorchidism (undescended testicles) and megaureters. The term has grown out of favor recently but was originally coined because the abdominal viscera can sometimes be seen through the thin abdominal wall.

Arthrogryposis multiplex congenital is a clinical term used to describe multiple congenital joint contractions which can occur in 1:3000 live births. It involves a diverse group of disorders and can affect multiple parts of the body. Treatment typically involves release of the contractures, as they can be painful and debilitating if not treated. **Congenital torticollis** is another important abnormality in muscle development where tearing of the sternocleidomastoid muscle fibers occurs during childbirth. Trauma from the birth canal can cause a hematoma to form in the muscle, causing compression of the local vasculature. This eventually leads to death of the muscle fibers surrounding the hematoma causing a shortening of the muscle on the side of injury. Clinically, the patient appears to laterally bend their head to the affected side. It is important to note that although birth trauma is the classic scenario for congenital torticollis, it is though that intrauterine crowding in multiple gestation pregnancies or primary myopathies can also lead to the condition.

Limb Formation

Although regulated by different genes, bone and muscle growth must occur in a coordinated fashion in order for proper development of the limbs. As we previously learned, the limb bud primordial structures appear at the end of the fourth week when somites appear on the ventrolateral body wall, however, most limb growth does not occur until the sixth week. Homeobox genes are essential in the regulation

of limb patterning. The limb buds themselves are formed by a serious of steps that begin with the formation of the somatopleure from the mesoderm. This structure is mesodermal tissue that abuts the ectodermal tissue at the ventrolateral surface of the embryo. The somatopleure's lateral mesoderm induces a thickening in the adjacent surface ectoderm causing a fold directly in front of the column of somites. The middle aspect of the column soon regresses leaving two swellings in the cervical and lumbar regions at the level of the future shoulder and pelvic girdles. A swelling of ectodermal tissue known as the apical ectodermal ridge arises on the proximal side of the column to induce the mesenchyme to grow and develop into a limb bud. Thus, the limb bud becomes a mass of mesenchymal tissue of somatic mesoderm origin, covered by surface ectoderm.

The first primordia of the upper limbs appear around 24 days of life with the lower limb lagging behind by 2 days. The distal ends of the limb buds begin to flatten into what become hand and foot plates in the sixth week. As week 6 progresses, the limb develops a proximal and distal segment. The proximal segment then begins to differentiate into two distinct pieces, forming ultimately three definitive segments per limb by the end of week 7. Chondroblasts migrate in the precartilaginous matrix in week 5 and eventually form the various skeletal parts of the limbs by the end of week 6 as well. Synovial joints can be seen by week 9. Ossification centers are present by week 12 and as the bones form and elongate, myoblasts aggregate and form the limb musculature as previously described.

In week 7 of life, the limbs move ventrally and begin rotation in opposite directions. Initially, the flexor surface is located ventrally with the extensor dorsal with the preaxial and postaxial borders being cranial and caudal, respectively. The upper limbs then rotate 90° laterally around their long axes so that the elbows face dorsally and extensor muscles move to the lateral and posterior aspect of the arm. The lower limbs then rotate medially 90° around their long axis so that the knees face ventrolaterally with the extensor muscles moving to the anterior aspects of the legs.

The innervation of the limbs is highly dependent on the growth and rotation of the limbs themselves. Peripheral spinal nerves begin to develop from the brachial plexi into the upper limb buds and the lumbosacral plexus into the lower limb buds in week 5. Sensory axons follow the motor axons entry into the limb buds and continue to grow with the limb. As the bud elongates, the nerves grow out along the limbs in an orderly fashion.

Disorders of Limb Development

The most essential period of limb development occurs from 24 to 36 days of life as the limb buds establish themselves and begin patterning. Abnormalities of the extremities can vary from relatively common minor limb malformations to major limb defects, which are more rare. Limb abnormalities can be isolated muscle or skeletal abnormalities previously described or can be more comprehensive, involving complete loss of segments of the limb. Most abnormalities are hereditary in

nature, caused by mutations or chromosomal factors. However, environmental influences have been described in widespread "outbreaks" such as occurred before the use of **thalidomide** was stopped in pregnant women. This potent teratogen was seen to cause severe limb defects if exposed to pregnant women during early pregnancy. Mechanical factors in utero can also cause limb abnormalities if the fetus is restricted or in the case of decreased amniotic fluid (oligohydramnios).

In the most extreme of cases, extremities can be completely absent (**Amelia**) or partially absent (**meromelia**) if limb development is disrupted in the fourth and fifth weeks, respectively. In some cases, the extremity is found to be normal but is shorter than expected, a condition known as **micromelia**. **Cleft hand or foot** is a rare disorder and occurs when 1 or more central digits are absent, resulting in a two-part hand/foot that resembles a lobster claw with the remaining digits fused together. Isolated **syndactyly** (fusion of digits) can also occur and is one of the most common limb malformations seen. It results from failure off two or more digits to differentiate into separate fingers when the process of apoptosis is disrupted. Syndactyly often occurs between digits 3 and 4. It can be autosomal dominant or recessive.

In **club hand**, also known as **congenital absence of the radius**, the radius is partly or totally absent and the hand deviates to the radial side with bowing of the ulna. This can be isolated or seen in certain syndromes, most notably TAR syndrome. In **talipes equinovarus** (better known as club foot), the sole of the foot is turned inwards causing adduction and plantar flexion of the foot at the mid-tarsal joint. This disorder is commonly seen in males and its severity can vary. A more severe birth defect known as **bifurcate hand and cleft foot** (clinically diagnosed as split hand/foot malformations) occurs when one or more central digits fails to develop. This autosomal dominant condition affects 1:20,000 live births and originates in the fifth to sixth week of development [3].

Brachydactyly is another genetic defect that occurs when there is abnormal shortening of the fingers or toes and reduction in size of the phalanges. It is often associated with short stature and can occur as an isolated disorder, with autosomal dominant inheritance or caused by specific gene mutations. Infants are sometimes found to have extra fingers or toes in **polydactyly**, a relatively common condition also caused by an autosomal dominant inheritance pattern. The supernumerary digit is typically useless, lacking muscle development. In the hand, it is often on the radial or ulnar side of the hand and when found on the foot, it is often on the fibular side.

Developmental dysplasia of the hips is often seen in females and associated with dislocation of the hips. It is associated with breech presentation and multiple gestations and leads to underdevelopment of the acetabulum of the head of the hip and head of the femur. **Sirenomelia** is another abnormality of the lower extremities in which the lower limbs become fused due to disturbance in the formation of the pelvis. The single lower extremity typically contains a single femur, 2–3 bones below the knee with 5–6 digits on the foot. This rare anomaly is seen with congenital diabetes and likely has a complex etiology of environmental and genetic factors.

References

1. Schoenwolf GC, Bleyl SB, Braur PR, Francis-West PH. Larsen's human embryology. 4th ed. Philadelphia, PA: Elsevier/Churchill Livingstone; 2014.
2. Cochard LR, Machado CG, Craig JA, Netter FH. Netter's Atlas of human embryology. Philadelphia: Saunders; 2012.
3. Moore KL, Persaud TVN, Torchia MG. The developing human: clinically oriented embryology. 8th ed. Philadelphia, PA: Saunders/Elsevier; 2011.

Chapter 2
Musculoskeletal Physical Examination of the Newborn

Sheila Chandran

Brief Overview

A thorough pediatric orthopedic assessment of the newborn can detect congenital abnormalities of the newborn. Interviewing the caregivers regarding prenatal birth and family history provides useful information to the examiner and allows them to pay careful attention for specific concerns. Prenatal history such as prenatal care visits, fetal ultrasound information, and the intra-uterine position of baby should be clarified. Birth history such as prematurity, birth weight, any perinatal complications, and length of hospital stay may provide clues for an underlying disorder. Family history of musculoskeletal disorders and neurological conditions should be asked for. A head-to-toe exam is performed, with the baby supine on an examining table, ideally down to a diaper. If the infant is crying, use of a pacifier or feeding may help facilitate the exam.

Clinical Presentation: History and Physical

General

The anatomy of the body is more or less symmetrical. Assess for obvious disparities of size, resting position, and movement of the limbs. Examine for muscle tone with flexing the elbows, knee, and ankles for overall tone and side to side comparison. Tone can be related to the infant's alertness. When holding a child under the axilla

S. Chandran (✉)
Department of Orthopedics, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA
e-mail: sheila.chandran@cchmc.org

J. F. Sarwark, R. L. Carl (eds.), *Orthopaedics for the Newborn and Young Child*,
https://doi.org/10.1007/978-3-031-11136-5_2

and lifting them, muscle tone of the shoulder girdle should be enough to support the child's weight. If a child slips through the examiners' grip, consider the presence of a neuromuscular disorder.

Head

Head shape and size are assessed. The forehead should be proportionate to the face with any bulging or distended venous structures noted. Fontanelles and sutures should be palpated looking for widening or premature fusing, as in craniosynostosis. Cranio-facial asymmetry or flattening of the face can be seen in torticollis. Examine the spacing and appearance of eyes. Outer ear deformities can be seen in genetic syndromes.

Neck

The neck should be looked at from the front and back. The neck should be passively rotated laterally towards each shoulder. The head should also be bent, to have the ear approach the ipsilateral shoulder. A low hairline can be seen in web neck deformities, Klippel-Feil syndrome, or Turner syndrome. In congenital torticollis, a mass may be palpated in the sternocleidomastoid muscle, along with restricted motion.

Shoulders/Clavicle/Scapula

Musculoskeletal pathology about the shoulder is less common than the other areas of the body. Reduced motion with fixed adduction and internal rotation can be seen in arthrogryposis. Pay careful attention to the rotation of the shoulder. In traction injuries of C5–C7, Erb's palsy, the upper extremity is held in internal rotation at the shoulder with elbow extended and hand pronated. The fingers will have normal motion. In Klumpke's palsy, the lower roots of C8-T1 are injured. The infant will have normal shoulder and elbow motion and position but the wrist and fingers will be in fixed flexion.

Swelling of the clavicle can be seen in birth trauma with a healing fractured clavicle or congenital pseudoarthrosis of the clavicle. Absence of clavicle may indicate skeletal dysplasia. Scapular size and symmetry should be checked. Winging of the scapula should be noted. Scapular hypoplasia can be seen in Sprengel deformity. If there is difficulty to abduct the shoulder to 180°, consider the possibility of Sprengel deformity.

Chest and Abdomen

Chest wall and ribs should be evaluated for pectus carinatum or excavatum. Abnormal chest development can be seen in Poland syndrome in which part of the pectoralis major is missing, causing the chest to appear concave.

Spine

Skin overlying the spine is examined for any cutaneous abnormalities, such as hypertrichosis (tufts of hair), hemangiomas, areas of hyperpigmentation or hypopigmentation. Mongolian spots are normal variations that can be seen on the spinal region. Presence of café au lait spots should be documented and other features of neurofibromatosis looked for (Fig. 2.1).

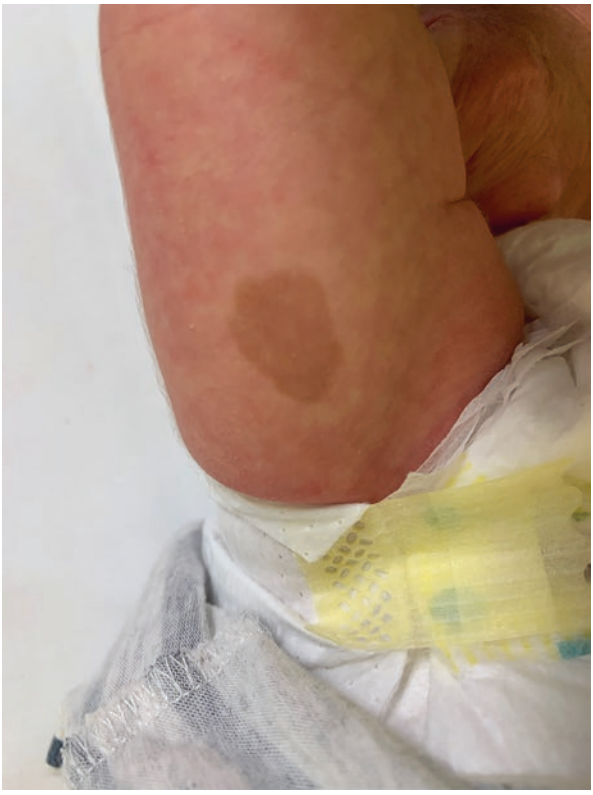


Fig. 2.1 Café au lait spot. Image courtesy of Rebecca L. Carl, MD

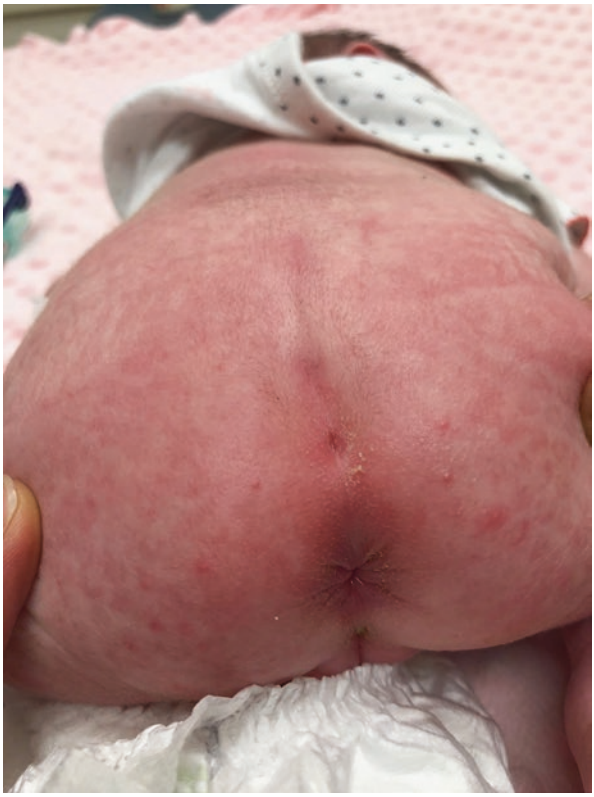


Fig. 2.2 Simple dimple

Simple sacral dimples are present in 3–5% of newborns are not associated with increased risk of neural tube defects or dermal sinus tracts [1]. Sacral dimples are considered simple if they are located within 2.5 cm of the anal verge, less than 0.5 cm in diameter, and are not associated with any other cutaneous abnormalities (Figs. 2.2 and 2.3). The presence of a deeper dimple above the gluteal cleft merits an ultrasound to evaluate for tethered cord and possible referral to pediatric neurosurgery.

Curvature of the spine is assessed by palpating the spinous processes and looking at waist symmetry.

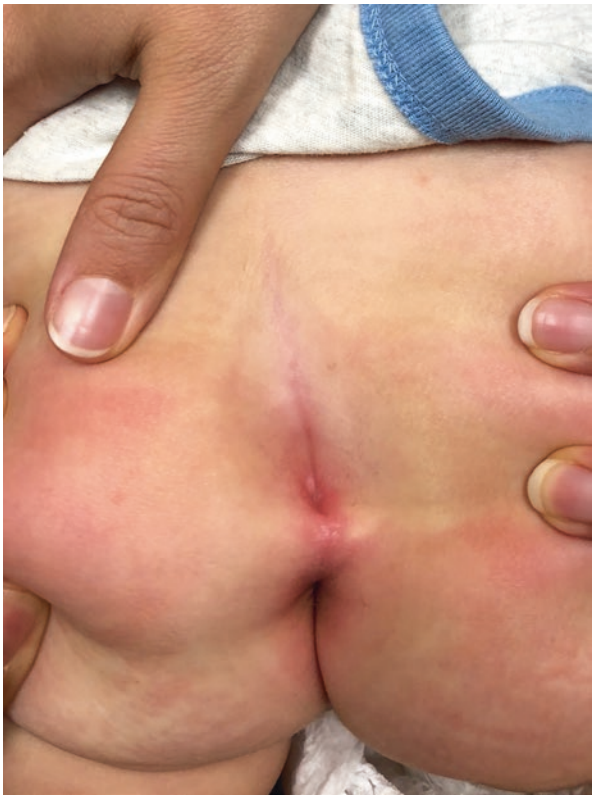


Fig. 2.3 Sacral dimple

Upper Extremity

Elbows

Motion of the elbow can be assessed with flexion and extension and supination and pronation of the forearm. Supination and pronation are typically 80–90°. Assess movement while palpating the radial head. Decreased movement could indicate radial head dislocation or congenital radioulnar synostosis.

Hands

Hands should be examined for the position, the appearance of the fingers and their motion. In newborns, the thumbs are often kept clasped and hand should be observed for movement. Limited wrist and finger flexion may indicate generalized condition such as arthrogryposis. There is failure of joint development in symphalangism, and fingers are flexed to various degrees. Clinodactyly with curvature of the fifth digit can be an isolated normal variant or seen in a variety of genetic conditions. Congenital amputation of fingers can be presentation of constriction/amniotic band syndrome. Polydactyly can also be an isolated finding but can be seen in other genetic abnormalities.

Brachysyndactyly with chest wall abnormalities is seen in Poland syndrome.

Hips

Infants should be examined when calm and relaxed. Even in newborns with extreme laxity, crying will tighten the musculature, potentially masking hip instability. Provocative maneuvers for hip stability are the Barlow and Ortolani tests. The Barlow maneuver attempts to dislocate the hip while the Ortolani relocates a dislocated hip. One hip should be tested at a time. In the Barlow maneuver, the examiners palm is on the knee and the femoral shaft is pushed downwards while the thumb pushes laterally on the medial proximal femur. A positive finding is the femoral head sliding out of the acetabulum with a palpable, and occasionally visible, clunk. In the Ortolani maneuver, the femoral head is gently lifted anteriorly into the acetabulum using the long finger. A positive finding again elicits a deep clunk. These sounds should be differentiated from hip clicks, which are common due to soft tissue structures moving over bony prominences.

Infants should have full and symmetric hip abduction and be able to achieve a wide “frog-leg” position of the hips. Decreased abduction may indicate a dislocated or subluxated hip. In bilateral hip dislocations, abduction may be symmetrical, but decreased. Asymmetry of the skin folds (especially proximally) may indicate hip dysplasia but has poor specificity.

Galeazzi testing should be done with the child lying supine with the pelvis level. The hips are flexed, and the knee heights are assessed. The Galeazzi test is positive when the knees are at different heights. This can indicate unilateral dislocated hip or a leg length discrepancy. Galeazzi test can be negative in bilateral dislocated hips (Figs. 2.4 and 2.5).

Fig. 2.4 Galeazzi

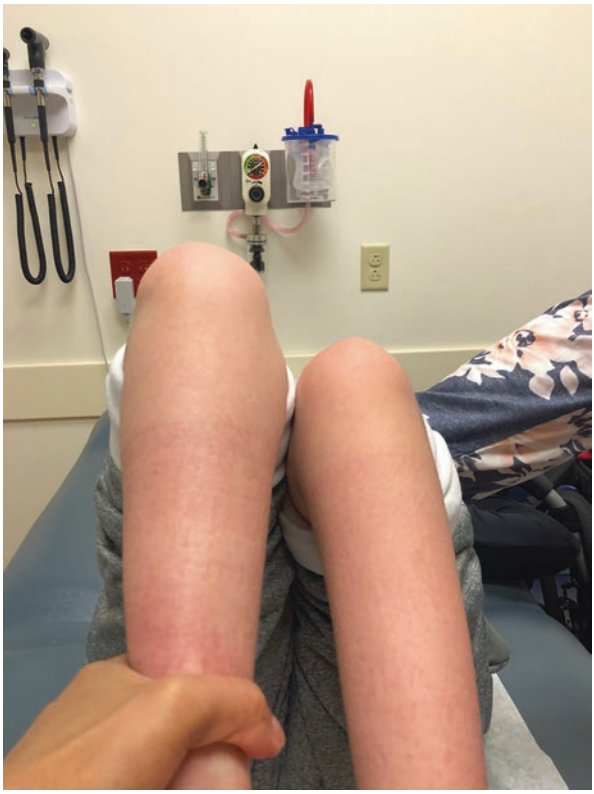


Fig. 2.5 Positive Galeazzi

Lower Extremity

Knees and Legs

Angular and torsional deformities can be looked for. The child should be examined in the supine position with patella facing forward and legs fully extended. This will avoid mistaking tibial torsion for genu varum. Feet will point inwards with internal tibial torsion.

In infants with positive Galeazzi, hemihypertrophy with enlargement of the thigh and/or calf musculature should be looked for.

Genu varum ("bowed legs") is normal in infants and toddlers. Children with genu varum that persists beyond age 2.5–3 years of age should be evaluated for an infantile tibia vara, bowing due to depression of the medial aspect of the tibial physis. Older toddlers and preschool-aged children typically exhibit genu valgum ("knock-knees").

A dimple seen along the anterior leg usually indicates a congenital abnormality, such as fibular hemimelia and is associated with anteromedial bowing. Anterolateral bowing of the tibia is associated with pseudoarthrosis and neurofibromatosis.

Posteromedial bowing of the tibia is associated with calcaneovalgus foot positioning. It can look severe at birth but frequently resolves during childhood. Posteromedial bowing often results in a leg length inequality that may require treatment. Fibrous dysplasia can also present with focal bowing of the femur or tibia.

Congenital dislocation of the knees is difficult to miss as the knees will be extended, with feet sometimes touching the face. Limited knee motion is also seen in lateral displacement of the patella.

Feet

Both active and passive motion of the feet and ankle are important to differentiate foot conditions. Curvature of the lateral border of the foot is seen in metatarsus adductus and congenital talipes equinovarus (clubfoot). Children with clubfoot have fixed plantarflexion at the ankles while those with metatarsus adductus have normal ankle dorsiflexion. Heel position will be in varus (inverted position) in cases of clubfoot (Figs. 2.6 and 2.7).

Fig. 2.6 Metatarsus adductus

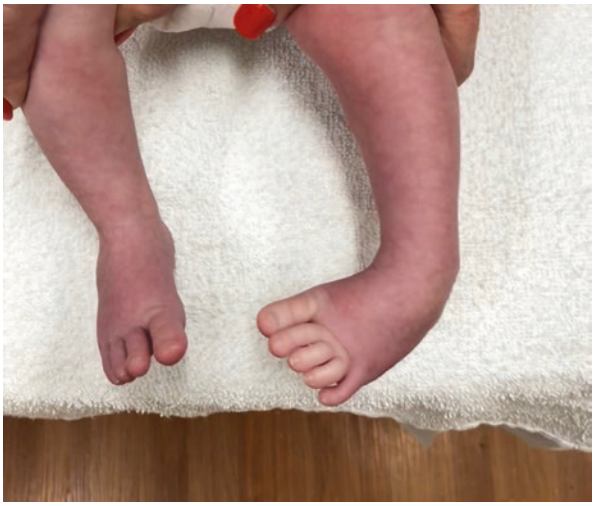


Fig. 2.7 Clubfoot

In infants, the medial longitudinal arch is decreased with most infants presenting with flexible flat feet. Pes cavus (high arch) in a child is associated with clubfoot. Isolated pes cavus may indicate a neurologic condition and requires further work up. A rocker bottom foot can be seen in congenital vertical talus. This rigid deformity should be differentiated from a calcaneovalgus foot deformity which is a benign flexible condition. Congenital vertical talus can be diagnosed with radiographs and will need orthopedic intervention (Fig. 2.8).

Toe anomalies such as simple partial syndactyly, overlapping or rotational changes are common.

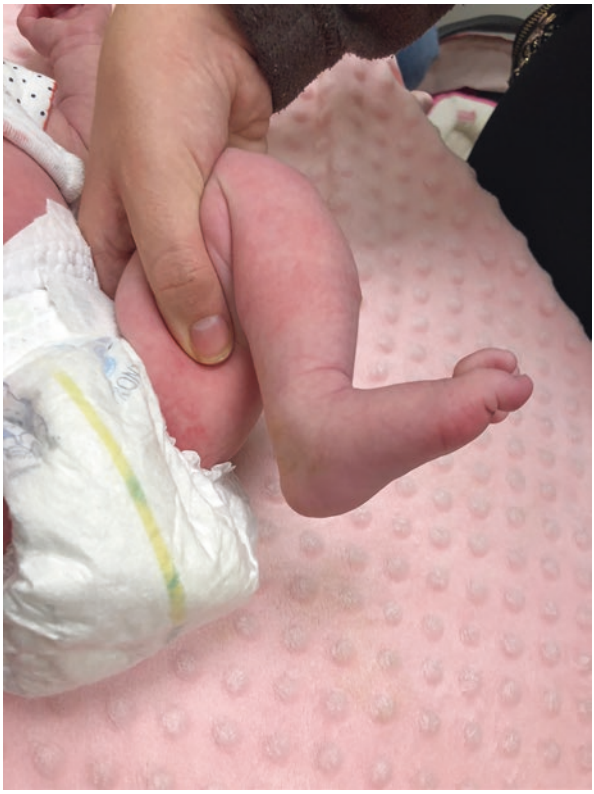


Fig. 2.8 Calcaneovalgus foot

Clinical Vignettes/Pearls

Careful observation of the baby while initial questions are being asked is helpful. If the infant starts crying, it is useful to have a pacifier or bottle ready to calm the child. Having a blanket to cover the portions of the body that is not being examined can also help to pacify the patient during the examination.

It is helpful to talk to the family about what is being examined and looked for as the physical exam is being conducted.

Once an infant is 3–4 months of age, ligamentous laxity decreases and Ortolani and Barlow test can become falsely negative. Careful evaluation of asymmetric hip abduction (indicating tight adductor muscles) or a positive Galeazzi (indicating a limb length discrepancy) should alert the examiner as a sign of developmental dysplasia of the hips (DDH).

The pelvis should be level on the exam table. Bundled blankets underneath the infant can confound the examiner.

Reference

1. Albert GW. Spine ultrasounds should not be routinely performed for patients with simple sacral dimples. Acta Paediatr. 2016;105(8):890–4.

Part II
Congenital and Developmental Disorders

Chapter 3
Metatarsus Adductus

Natalie C. Stork

Brief Overview of Condition

Metatarsus adductus is a common foot anomaly, often diagnosed in infancy [1]. The deformity primarily affects the forefoot, producing a characteristic shape to the foot [2–5].

In 1921, orthopedic surgeons in Europe began to describe a deformity distinct from clubfoot [6]. This deformity, unlike clubfoot, appeared to only affect the forefoot. It was characterized by an adducted forefoot relative to a normal hindfoot and was termed metatarsus varus. By the 1930s, Charles Peabody and Felipe Muro had investigated metatarsus varus in the United States and agreed, there was a deformity separate from clubfoot in which the forefoot was adducted [6]. Since that time various terms have been used to describe a similar deformity. Metatarsus adductus is commonly used today to describe a congenital foot anomaly in which the forefoot (the metatarsals and phalanges) is medially deviated or adducted relative to the hindfoot. The hindfoot is generally neutral or positioned in mild valgus. Unlike clubfoot, there is normal motion through the ankle joint, without evidence of equinus (plantar flexion) contracture [2, 6–10].

N. C. Stork (✉)
Department of Orthopaedic Surgery and Musculoskeletal Science, Children's Mercy Hospital Kansas City, Kansas City, MO, USA

Departments of Orthopaedic Surgery and Pediatrics, University of Missouri-Kansas City School of Medicine, Kansas City, MO, USA
e-mail: ncstork@cmh.edu

J. F. Sarwark, R. L. Carl (eds.), *Orthopaedics for the Newborn and Young Child*,
https://doi.org/10.1007/978-3-031-11136-5_3

Background Including Epidemiology and Pathophysiology

Metatarsus adductus is one of the most common foot anomalies of infancy, with the incidence estimated at about 1 per 1000 live births [1]. Hunziker et al. reported an incidence around 12% in full term singleton live births with a higher incidence in twin births [11]. The deformity appears to occur at the tarsal-metatarsal joints of the foot. While the true etiology is not well understood, various authors have suggested different theories [4, 10, 12, 13]. Intrauterine positioning had been suggested as one of the common theories. The increased incidence in twin gestation and spontaneous resolution in 85–90% of cases supports this idea [2, 10]. Asymmetric muscular forces or anomalous muscle/tendon attachments have also been proposed [6, 13]. Finally, an abnormal shape of the medial cuneiform has also been entertained as playing a role in the deformity [6, 12, 13]. However, while osseous differences and variability in muscle attachments have been described, it is not clear whether these differences are causative or adaptive changes. Thus, the true etiology of metatarsus adductus remains unknown.

Clinical Presentation: History and Physical

Metatarsus adductus is often noticed within the first year of life. Depending on time of presentation to clinic, parents may have noticed improvement since birth. On appearance, the forefoot (the metatarsal) is adducted relative to the hindfoot (the calcaneus and talus). Unlike clubfoot and other foot anomalies, the deformity appears more isolated to the forefoot, while the hindfoot remains neutral or in mild valgus [5–10, 14]. There is no equinus contracture, thus normal motion at the ankle joint, i.e., normal dorsiflexion and plantar flexion. Looking at the sole of the foot, there is a convex appearance to the lateral border with concave appearance medially [2, 9, 13, 15]. Authors have described the foot as looking like a “C” or having a bean shape (Fig. 3.1) [2–5]. There may also be visible prominence of the fifth metatarsal or cuboid, mild supination of the foot, and a medial crease through the longitudinal arch [3, 4, 9, 10, 12].

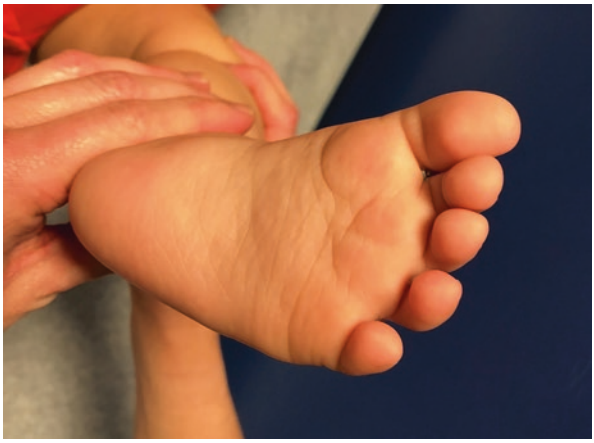


Fig. 3.1 Metatarsus adductus in infant, with mild convex appearance to the lateral border and prominence of the base of the fifth metatarsal

Evaluation

In addition to the classic visual appearance to metatarsus adductus, there are two methods commonly used to help characterize the deformity at time of diagnosis. Bleck wrote about two separate objective measures to look at severity and flexibility of the deformity [7]. The heel bisector method was initially described as looking at a photocopy of the affected foot and drawing a line bisecting the heel in two and then extending this line through the forefoot. Severity was determined by looking at where the line intersected the toes. The heel bisector intersected the second web-space in normal feet. In mild deformities, the heel bisector intersected the third toe (Fig. 3.2). The heel bisector fell between the third and fourth toes OR the fourth toe in moderate deformities (Fig. 3.3). Finally, severe deformities demonstrated a heel bisector falling between the fourth and fifth toes or farther lateral [7, 16, 17]. This has often been modified in practice by looking at the sole of the foot and drawing an imaginary line bisecting the heel up through the toes while using the same classification system described above to report on mild, moderate, or severe deformity.

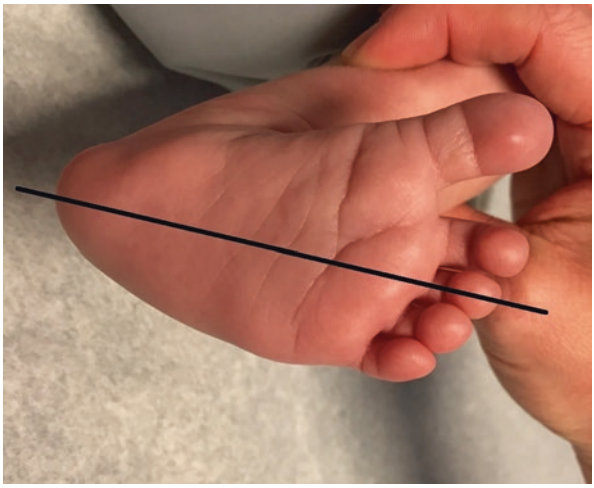


Fig. 3.2 Mild metatarsus adductus, heel bisector intersects the third toe

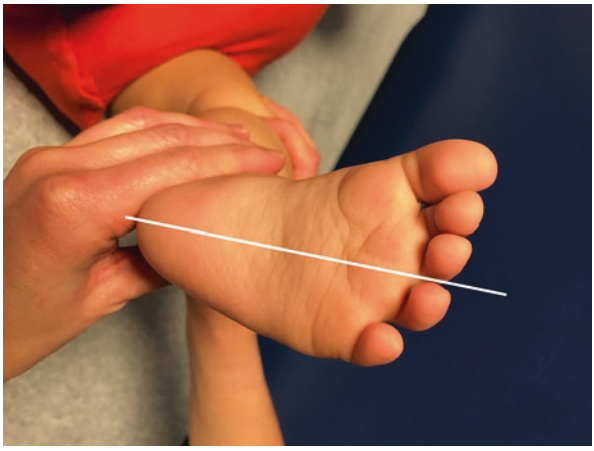


Fig. 3.3 Moderate metatarsus adductus, heel bisector intersects the third and fourth toes, the third web space

To further characterize flexibility, Bleck describes the amount of passive abduction of the forefoot achieved in reference to the heel bisector. To assess flexibility, the provider holds the hindfoot in a neutral position, gentling abducting the forefoot. With flexible deformities, the provider should be able to gently abduct the forefoot past midline, with the heel bisector extending beyond normal (i.e., extending through the second toe or first webspace) (Fig. 3.4). Partially flexible deformities were described as deformities that with passive flexion, the heel bisector corrected solely to midline (between the second and third toes). Finally, rigid or inflexible deformities are described as inability to passively correct the heel bisector or inability for the forefoot to abduct [7, 17].

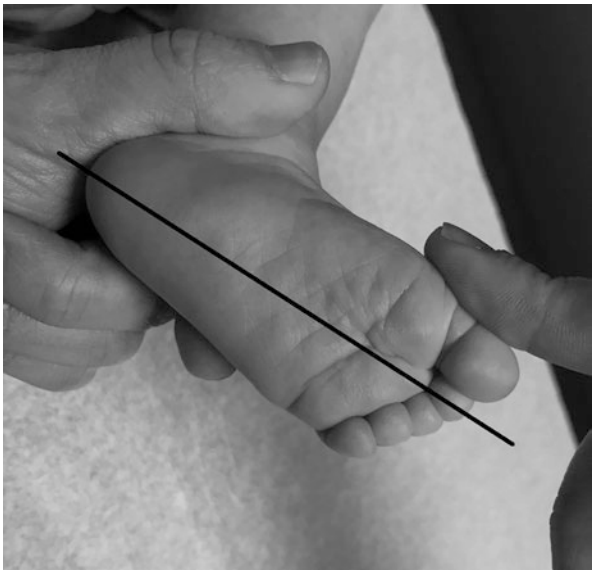


Fig. 3.4 Flexible metatarsus adductus; with gentle abduction of the forefoot, the heel bisector corrects past normal, intersecting the second toe

A full clinical orthopedic exam is recommended at time of diagnosis looking at range of motion through all limbs, any abnormal posturing, the shape of the spine, sacral cutaneous lesions, cervical spine range of motion, and a thorough clinical exam of the hips. Literature has reported various incidence of hip dysplasia with metatarsus adductus ranging from 1.5 to 10%, with the more recent literature reporting lower incidence [18–20]. While routine radiographic screening is generally not recommended for isolated metatarsus adductus without other risk factors, a thorough clinical screening exam is recommended with the decision for further imaging based on exam and risk factors.

Metatarsus adductus remains a clinical diagnosis at this time, thus regular radiographs are generally not necessary to make the diagnosis. Berg described a radiographic classification system using anteroposterior (AP) and lateral standing or simulated weight bearing radiographs in infants ranging between 2 and 17 months of age [21]. Cook et al., however, demonstrated poor intra-observer and inter-observer reliability with the same classification system. In addition, this system did not appear to provide a reliable correlation between the radiographic classification and the length of time needed for manipulation and stretching casts [22].

Radiographs should be considered in children and adolescents with pain, residual deformity, and or other symptoms or disability. Radiographs of residual deformity will likely demonstrate an oblique positioning of the medial cuneiform with associated adduction of the metatarsal bones. The hindfoot alignment oftentimes remains normal in radiographs [10, 12].

Management

While there is limited evidence on the true efficacy of suggested treatment options, a few authors have provided what we currently know and accept regarding treatment of metatarsus adductus. Treatment options include home stretching exercises conducted by the parents, braces or corrective shoes, stretching casts, and a variety of operative options, which will not be discussed at this time.

Multiple authors have reported on the spontaneous correction often observed in the mild flexible deformities [2, 3, 5, 8, 10, 12, 13, 15]. Thus, reassurance to the family is often all that is needed in cases of mild flexible metatarsus adductus.

The effectiveness of passive stretching exercises has not been well described in the literature [9, 10, 13, 23]. Some authors raise concern that improper stretching may in fact be harmful, leading to hindfoot valgus and flatfoot deformity [15, 23]. Literature regarding the efficacy of corrective shoes and braces is also lacking. Similar concerns regarding the complication of creating a valgus deformity of the hindfoot, due to incorrect position of pressure counterpoints, exist with use of a foot-abduction type brace often used for maintaining correction in clubfoot deformities [15, 21].

Several authors have described the efficacy of serial manipulations and casting in the treatment of moderate to severe, partially flexible and rigid metatarsus adductus [2, 5, 7, 10, 12–15, 21, 24]. The timing on when to initiate casting is still somewhat variable with recommendations ranging from 3 to 12 months of age [2, 5, 7, 8, 10, 12]. As with clubfoot casting and other manipulative serial casting, there is added technique required to assure the provider is addressing the deformity. When manipulating the foot and applying the cast, care must be taken to avoid any excessive valgus stress of the hindfoot [9, 10, 15]. Given the age and body habitus of infants, long leg casts are recommended. The number of serial casts may vary with average reported by some authors at about four and duration between cast changes varying between 1 and 2 weeks [15]. Recurrence of the deformity has been described by some authors, thus continued clinical follow-up after manipulation and casting is recommended [16, 25]. The efficacy of post casting splints, shoes, or bracing is again not well described in the literature.

Surgical correction is rarely ever indicated. Consideration for surgical referral could be considered in an older child (i.e., greater than 3 or 4 years of age) with moderate to severe residual deformity, pain, or other disability [5, 10].

Clinical Vignettes/Clinical Pearls

- Deformity primarily affects the forefoot, with the metatarsals medially deviated relative to the hindfoot
- Normal passive dorsiflexion of the foot and ankle

- Mild, flexible deformities will typically spontaneously improve
- Persistent, partially flexible or rigid deformities warrant referral to an orthopedic specialist

Natural History, Primary and Secondary Prevention

As mentioned above, many authors have described the spontaneous correction that occurs in the vast majority of mild, flexible metatarsus adductus with 85–90% resolution within the first year of life [2, 3, 15]. There are few studies looking that describe longer term follow-up with metatarsus adductus. Rushforth prospectively looked at children in follow-up, average age 7 years old, who received no treatment for metatarsus adductus. Of the 130 feet he evaluated in 83 children, he found that the majority 86% demonstrated a normal appearance or mild residual deformity with normal motion. He did observe persistent moderate deformity in about 10% of these children, however they were asymptomatic. In addition, he describes 4% of children with residual deformity that was stiff though does not comment on any associated symptoms [26]. Farsetti et al. demonstrated similar results looking at a smaller group of patients over a longer duration of follow-up (average follow-up of 32 years). Follow-up of these patients also demonstrated a positive outcome, with 90% (26 of 29 feet) reporting good results with a normal appearance of the foot. Only 3 of 29 feet were described as fair results, with mild residual deformity without significant functional limitations. There were no poor results [12]. While there is limited evidence regarding potential long-term effects of residual deformity in adulthood, studies that do provide follow-up reported few poor results and operative management was generally not indicated [2, 5, 10, 12, 26].

References

1. Wynne-Davies R, Littlejohn A, Gormley J. Aetiology and interrelationship of some common skeletal deformities. (Talipes equinovarus and calcaneovalgus, metatarsus varus, congenital dislocation of the hip, and infantile idiopathic scoliosis). J Med Genet. 1982;19(5):321–8.
2. Dietz FR. Intoeing—fact, fiction and opinion. Am Family Physician. 1994;50(6):1249–59, 62–4.
3. Gore AI, Spencer JP. The newborn foot. Am Fam Physician. 2004;69(4):865–72.
4. Marshall N, Ward E, Williams CM. The identification and appraisal of assessment tools used to evaluate metatarsus adductus: a systematic review of their measurement properties. J Foot Ankle Res. 2018;11:25.
5. Sankar WN, Weiss J, Skaggs DL. Orthopaedic conditions in the newborn. J Am Acad Orthopaed Surg. 2009;17(2):112–22.
6. Kane R. Metatarsus varus. Bull NY Acad Med. 1987;63(9):828–34.
7. Bleck EE. Metatarsus adductus: classification and relationship to outcomes of treatment. J Pediatr Orthoped. 1983;3(1):2–9.
8. Bohne W. Metatarsus adductus. Bull NY Acad Med. 1987;63(9):835–8.
9. Kite JH. Congenital metatarsus varus. J Bone Joint Surg Am. 1967;49(2):388–97.

10. Mosca V. The foot. In: Weinstein S, Flynn J, editors. Lovell and winter's pediatric orthopaedics. 2. 7th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2014. p. 1388–525.
11. Hunziker UA, Largo RH, Duc G. Neonatal metatarsus adductus, joint mobility, axis and rotation of the lower extremity in preterm and term children 0-5 years of age. Eur J Pediatr. 1988;148(1):19–23.
12. Farsetti P, Weinstein SL, Ponseti IV. The long-term functional and radiographic outcomes of untreated and non-operatively treated metatarsus adductus. J Bone Joint Surg Am. 1994;76(2):257–65.
13. Williams CM, James AM, Tran T. Metatarsus adductus: development of a non-surgical treatment pathway. J Paediatr Child Health. 2013;49(9):E428–33.
14. Sielatycki JA, Hennrikus WL, Swenson RD, Fanelli MG, Reighard CJ, Hamp JA. In-toeing is often a primary care orthopedic condition. J Pediatr. 2016;177:297–301.
15. Ponseti IV, Becker JR. Congenital metatarsus adductus: the results of treatment. J Bone Joint Surg Am. 1966;48(4):702–11.
16. Bleck EE. Developmental orthopaedics. III: Toddlers. Devel Med Child Neurol. 1982;24(4):533–55.
17. Smith JT, Bleck EE, Gamble JG, Rinsky LA, Pena T. Simple method of documenting metatarsus adductus. J Pediatr Orthoped. 1991;11(5):679–80.
18. Kumar SJ, MacEwen GD. The incidence of hip dysplasia with metatarsus adductus. Clin Orthopaed Related Res. 1982;164:234–5.
19. Paton RW, Choudry Q. Neonatal foot deformities and their relationship to developmental dysplasia of the hip: an 11-year prospective, longitudinal observational study. J Bone Joint Surg Br. 2009;91(5):655–8.
20. Jacobs JE. Metatarsus varus and hip dysplasia. Clin Orthop. 1960;16:203–13.
21. Berg EE. A reappraisal of metatarsus adductus and skewfoot. J Bone Joint Surg Am. 1986;68(8):1185–96.
22. Cook DA, Breed AL, Cook T, DeSmet AD, Muehle CM. Observer variability in the radiographic measurement and classification of metatarsus adductus. J Pediatr Orthoped. 1992;12(1):86–9.
23. Eamsobhana P, Rojjananukulpong K, Ariyawatkul T, Chotigavanichaya C, Kaewpornsawan K. Does the parental stretching programs improve metatarsus adductus in newborns? J Orthop Surg (Hong Kong). 2017;25(1):2309499017690320.
24. Katz K, David R, Soudry M. Below-knee plaster cast for the treatment of metatarsus adductus. J Pediatr Orthoped. 1999;19(1):49–50.
25. McCauley J Jr, Lusskin R, Bromley J. Recurrence in Congenital Metatarsus Varus. J Bone Joint Surg Am. 1964;46:525–32.
26. Rushforth GF. The natural history of hooked forefoot. J Bone Joint Surg Br. 1978;60-b(4):530–2.

Chapter 4
Calcaneovalgus

Natalie C. Stork

Brief Overview of Condition

Calcaneovalgus is a common foot anomaly of infancy characterized by marked dorsiflexion at the ankle joint. The etiology is unknown, though it is thought to be secondary to intrauterine positioning [1–4]. It is often benign in nature and requires little in way of treatment.

Background Including Epidemiology and Pathophysiology

Reports of the incidence of calcaneovalgus have varied in the literature. Wynne-Davies reported an incidence similar of around 1/1000 live births [5]. Wetzenstein however reported an incidence of 30–50% [6]. The rather benign nature of this foot anomaly and high spontaneous resolution rate likely contribute to the wide variability in reported incidence. The true etiology of calcaneovalgus is not known, though intrauterine positioning is thought to contribute [1–4].

N. C. Stork (✉)
Department of Orthopaedic Surgery and Musculoskeletal Science, Children's Mercy Hospital Kansas City, Kansas City, MO, USA

Departments of Orthopaedic Surgery and Pediatrics, University of Missouri-Kansas City School of Medicine, Kansas City, MO, USA
e-mail: ncstork@cmh.edu

J. F. Sarwark, R. L. Carl (eds.), *Orthopaedics for the Newborn and Young Child*,
https://doi.org/10.1007/978-3-031-11136-5_4

Clinical Presentation

Upon physical examination, a calcaneovalgus foot demonstrates a significant amount of dorsiflexion [2, 3, 6–8]. The dorsal aspect of the foot may be pressed against the anterolateral aspect of the shin and there may a subtle indentation around the sinus tarsi (Fig. 4.1). The calcaneus, or hindfoot, demonstrates a varied amount of valgus. With passive plantarflexion and inversion, there is often some limitation with mild contractures of the associated soft tissue structures [2, 4, 7–9]. Despite this limitation in motion, the hindfoot and midfoot are generally able to be positioned in a corrected position.

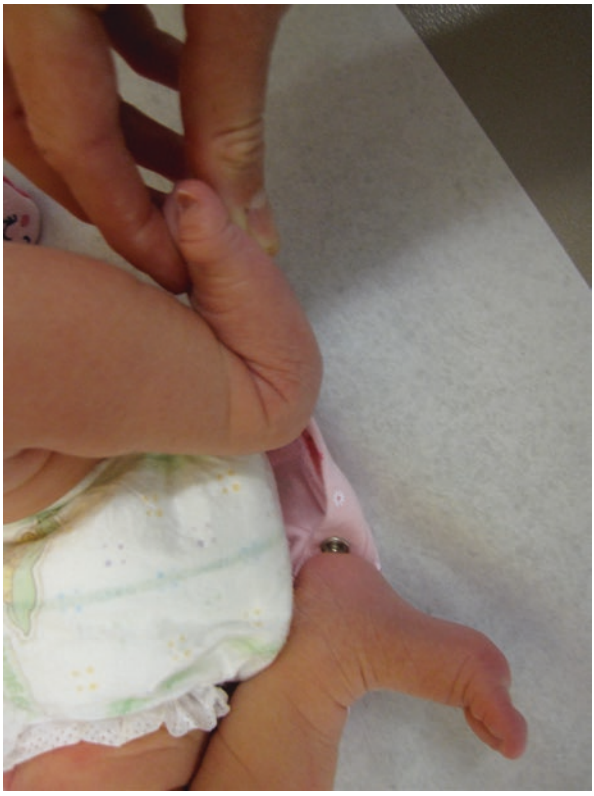


Fig. 4.1 Calcaneovalgus of the left foot demonstrating excessive dorsiflexion, everted ankle position, and prominence of the medial malleolus. Image courtesy of Rebecca L. Carl, MD

Evaluation

Calcaneovalgus, like other benign foot anomalies of infancy, is a clinical diagnosis. Radiographs are generally not necessary to make the diagnosis; however, imaging may be helpful when there is question of congenital vertical talus and/or posteromedial bowing of the tibia (Fig. 4.2) [2, 8]. When trying to differentiate between positional calcaneovalgus and vertical talus, an anterior-posterior (AP) and lateral radiographs (a lateral with the foot in maximal plantarflexion and one with the foot in maximal dorsiflexion) of the foot may be beneficial. When assessing for posteromedial bowing of the tibia, an AP and lateral view of the tibia/fibula will help determine whether or not there is a bow to the underlying tibia.

A full orthopedic screening exam should be conducted when evaluating a patient with concern for calcaneovalgus. Paton and Choudry demonstrated a higher risk of hip dysplasia in infants with congenital calcaneovalgus relative to other foot anomalies [10]. While routine radiographic screening of the hips in an infant with isolated positional calcaneovalgus without other risk factors is generally not recommended at this time, a thorough clinical screening exam is recommended. The decision for further radiographic imaging should be based on clinical exam and risk factors.

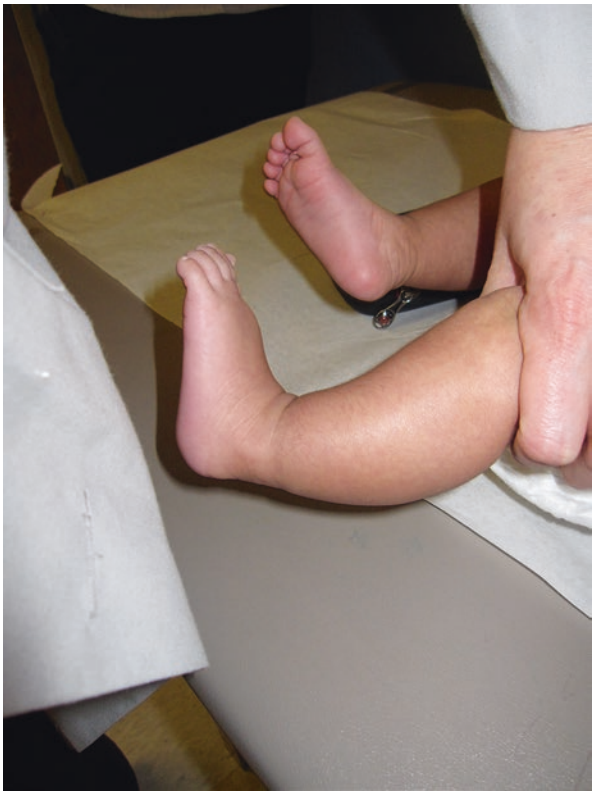


Fig. 4.2 Posteromedial bowing of the tibia/fibula, which can be associated with calcaneovalgus foot and ankle position. Image courtesy of Rebecca L. Carl, MD

Management

Treatment of calcaneovalgus is often minimal [2, 5, 8]. Larsen et al. demonstrated that there was no difference in patients that underwent manipulations and stretching bandages vs patients with whom were clinically monitored [8]. In an attempt to provide some treatment options, gentle stretching exercises can be demonstrated for the parents, however there is no literature to support the efficacy of a home stretching routine. It is a very rare occasion that stretching casts or surgery would be indicated [2].

Clinical Vignettes/Clinical Pearls

Calcaneovalgus is characterized by excessive dorsiflexion with mild limitation in plantarflexion.

It is a flexible anomaly, and the foot can be positioned in a neutral position easily.

The provider should rule out other causes of increased dorsiflexion, i.e., congenital vertical talus, posteromedial bowing of the tibia.

Prognosis for positional calcaneovalgus is generally excellent.

Natural History, Primary and Secondary Prevention

The natural history of positional calcaneovalgus is generally benign with a great prognosis [2, 8].

References

1. Giannestras NJ. Static deformities of the foot—editorial comment. Clin Orthop Relat Res. 1970;70:2–3.
2. Mosca VS. The foot. In: Weinstein SL, Flynn JM, editors. Lovell and winter's pediatric orthopaedics. 2. 7th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2014. p. 1499–500.
3. Nunes D, Dutra MG. Epidemiological study of congenital talipes calcaneovalgus. Braz J Med Biol Res. 1986;19(1):59–62.
4. Storen H. Congenital convex pes valgus with vertical talus. Acta Orthop Scand. 1967;Suppl 94:1–104.
5. Wynne-Davies R, Littlejohn A, Gormley J. Aetiology and interrelationship of some common skeletal deformities. (Talipes equinovarus and calcaneovalgus, metatarsus varus, congenital dislocation of the hip, and infantile idiopathic scoliosis). J Med Genet. 1982;19(5):321–8.
6. Wetzenstein H. Prognosis of pes calcaneo-valgus congenitus. Acta Orthop Scand. 1970;41(1):122–8.
7. Ferciot CF. Calcaneovalgus foot in the newborn and its relation to developmental flatfoot. Clin Orthop. 1953;1:22–7.

8. Larsen B, Reimann I, Becker-Andersen H. Congenital calcaneovalgus:with special reference to treatment and its relation to other congenital foot deformities. Acta Orthop Scand. 2009;45(1–4):145–51.
9. Giannestras NJ. Recognition and treatment of flatfeet in infancy. Clin Orthop Relat Res. 1970;70:10–29.
10. Paton RW, Choudry Q. Neonatal foot deformities and their relationship to developmental dysplasia of the hip: an 11-year prospective, longitudinal observational study. J Bone Joint Surg Br. 2009;91(5):655–8.

Chapter 5
Congenital Talipes Equinovarus (Clubfoot)

Melissa A. Bent

Clubfoot (and Positional Equinovarus)

Brief Overview

Clubfoot or congenital talipes equinovarus (TEV) is a complex disorder of the leg, foot, and ankle. Clubfoot may be idiopathic or associated with a syndrome or neuromuscular condition. Over the past two decades, initial clubfoot management has changed drastically as the minimally invasive Ponseti technique has become the standard of care. The Ponseti method consists of three phases: serial casting, Achilles tendon release (for the majority of patients), and bracing to maintain correction. The first phase involves serial manipulation and casting, typically performed weekly for an average of about five casts. Most infants require a minimally invasive surgical procedure to cut the Achilles tendon (tenotomy) in order to correct residual equinus deformity. The third phase consists of bracing with a brace that consist of two shoes connected by a bar. This device is worn full time for a short period with subsequent nighttime wear until the patient is about 4 years old. Patients have done well with this approach with excellent long-term results. The Ponseti method can be employed for patients with more severe cases of clubfoot secondary to genetic syndromes, neuromuscular conditions, or those with neglected clubfoot; however, these patients have higher rates of recurrence.

Supplementary Information The online version contains supplementary material available at [https://doi.org/10.1007/978-3-031-11136-5_5].

M. A. Bent (✉)
Department of Orthopaedic Surgery, Children's Hospital of Los Angeles, Los Angeles, CA, USA
e-mail: mbent@chla.usc.edu

J. F. Sarwark, R. L. Carl (eds.), *Orthopaedics for the Newborn and Young Child*,
https://doi.org/10.1007/978-3-031-11136-5_5

Recurrence is common with TEV with 25% of patients requiring additional casting, bracing, and/or subsequent surgery. Nonadherence to the bracing regimen is the factor most commonly associated with recurrent deformity.

The foot is never completely normal but the goal of treatment is to obtain a plantigrade, functional pain free foot. There is a promising future for understanding the etiology and genetic basis of clubfoot and continuing to improve access to and evolve treatment options for these patients and their families.

Some patients have a very mild equinovarus deformity. Positional or postural equinovarus is the term used to describe TEV that develops later in pregnancy, likely related to *in utero* positioning. Positional clubfoot resolves either spontaneously, with manipulation alone, or with a brief period of casting.

Epidemiology

The birth prevalence of clubfoot is 1 per 1000 live births [1]. Globally, in low- and middle-income countries, the birth prevalence reported is 0.51 and 2.03/1000 live births [2]. Idiopathic clubfoot is bilateral in half of cases. It affects boys about twice as often as girls. Twin studies, differences in the incidence among various ethnic groups, and positive family history all suggest a genetic component to clubfoot [3]. Certain ethnic groups have a predisposition to clubfoot. In Pacific Islanders, the incidence is nearly 7 per 1000 [4, 5]. Eighty percent of clubfoot cases are isolated while the remainder of cases is associated with conditions such as myelodysplasia, arthrogryposis, and other syndromes [6].

Clubfoot is a heterogeneous disorder with polygenetic inheritance. A quarter of all patients with clubfoot report a positive family history. For counseling parents of children with clubfoot, there is 17 times higher likelihood than the general population if first degree relative has clubfoot and six times higher in a second degree relative [7]. There is higher concordance in identical compared to fraternal twins with 2.9 risk in fraternal twins similar to other siblings compare to 32.5 in identical twins [8, 9].

There are many theories on the pathogenesis of clubfoot including in utero molding, in utero immobility, connective tissue fibrosis or primary muscle, bone, vascular, or nerve anomalies [10–13]. Others have looked at environmental factors such as maternal smoking [14]. None of these theories has a genetic basis.

There have been recent studies that have identified a genetic factor associated with clubfoot. The PITX1-TBX4-HOXC transcription pathways are critical for hindlimb development to play a role in clubfoot etiology but no single gene has yet

to be identified [15–17]. Understanding the etiology can help to improve genetic counseling for affected families, provide insight into normal limb development and opportunity to impact treatment.

Normal Foot Anatomy

The foot is divided into the forefoot, midfoot, and hindfoot. The forefoot consists of the toes and metatarsals, the midfoot consists of the navicular, cuboid, and cuneiform, and the hindfoot consists of the talus and calcaneus.

The ankle consists of the tibia, the fibula, and the talus. It allows for dorsiflexion (upward) and plantarflexion (downward motion of the foot and ankle). The subtalar joint between the talus and the calcaneus allows inversion and eversion of the ankle.

The term "equinovarus" describes the foot position seen in infants with clubfoot. Equinus refers to an ankle joint that is stuck in plantarflexion. Hindfoot varus means the calcaneus/heel inverts towards the midline. Children with clubfoot also have cavus deformity (high arch).

Pathophysiology

Clubfoot is not solely a deformity of the foot but a deformity of the entire lower extremity distal to the knee. In individuals with unilateral clubfoot, the affected side tends to have a smaller foot and calf and a stiffer and weaker ankle. Leg length discrepancy can also be seen but clinically significant shortening of the affected limb is uncommon [18, 19]. Fetal dissections showed that the muscles are smaller and shorter in clubfoot [11, 20].

There is both bony and soft tissue pathology of the foot. It was an understanding of the functional anatomy that led to the Ponseti method identifying the correct steps towards correction of the clubfoot deformity. The Ponseti method employs a systematic approach to manipulation of the foot in order to correct the various components of clubfoot deformity. The mnemonic CAVE (cavus, adductus, varus, equinus) is helpful to remember the components of the deformity and the order in which the components are corrected (Fig. 5.1).

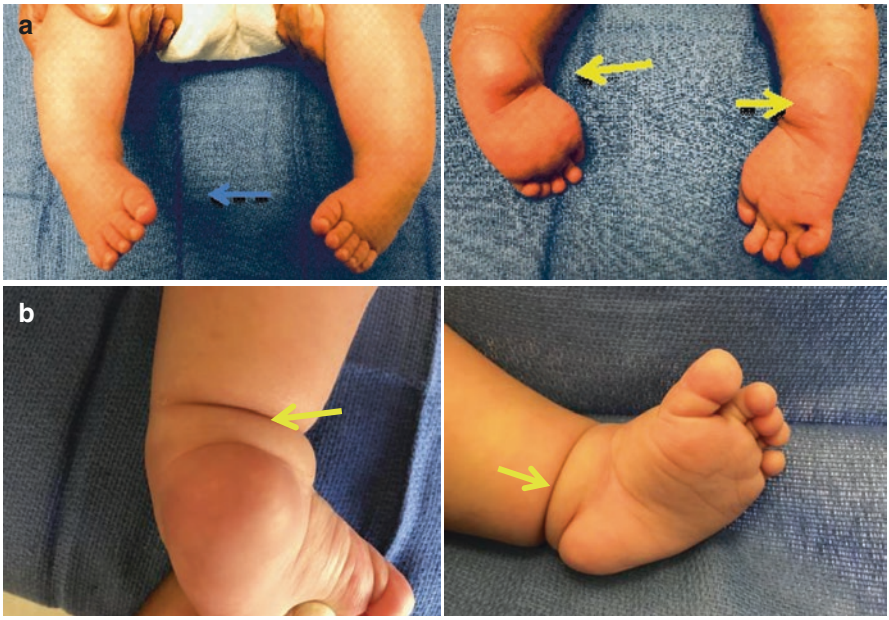


Fig. 5.1 (**a**) Anterior and posterior views of the forefoot cavus and adductus (blue arrow) and hindfoot varus and equinus. Note the deep medial crease (yellow arrow). (**b**) Note hindfoot varus (heel pointed toward the midline) and the single posterior heel crease (posterior and medial views)

Common Clinical Presentation: History and Physical

The newborn examination of any infant with concern for clubfoot should begin with a complete examination of the child, with examination of the foot being last. Clinicians should evaluate the head and neck for plagiocephaly and torticollis. The examiner should evaluate the spine, muscle tone, and look for any neurocutaneous lesions that could signal the presence of an underlying neuromuscular condition or syndrome. All upper extremity and lower extremity joints should be assessed to look for joint contractures. The physical examination should include a complete hip examination to assess for developmental dysplasia of the hip. There is an association with metatarsus adductus, torticollis, and developmental dysplasia of the hip secondary to intrauterine molding. Clubfoot is not associated with developmental dysplasia of the hip as previously thought; however, primary care physicians may find it difficult to assess the hips at routine health supervision visits once casting has begun [21, 22].

On physical examination of the foot, one must be able to distinguish between metatarsus adductus, positional equinovarus, and structural clubfoot. Forefoot adductus is one component of clubfoot; children with isolated metatarsus adductus will not have the other structural features of TEV.

In infants with metatarsus adductus, the forefoot (toes and metatarsals) is adducted. If the examiner draws a line between the heel and the toes known as the "heel bisector," this normally intersects between second and third toes. In metatarsus adductus, the heel bisector is lateral between the third and fourth or fourth and fifth toes. There are three main findings on exam that support a diagnosis metatarsus adductus compared to clubfoot: (1) normal ankle dorsiflexion, (2) neutral heel alignment with a flexible subtalar joint that allows the heel to be passively stretched into valgus, and (3) the lateral border of the foot is curved ("kidney bean shaped").

In positional clubfoot, the foot rests in a clubfoot position. However, the foot and ankle are flexible and can be passively stretched into a dorsiflexed, everted position. Additionally, children with unilateral positional clubfoot will not have a foot or calf muscle size discrepancy as is seen with idiopathic clubfoot.

With structural/idiopathic clubfoot, the following anatomic features are typically seen: forefoot adductus, cavus (high arch), hindfoot varus, ankle equinus, prominent head of the talus, single posterior crease in the back of the heel, midfoot crease, small foot size on the affected side(s), and rigidity of the foot. The presence or absence of these features is used in clinical classification to determine the severity of the clubfoot. The DiMeglio and Pirani classifications are the most commonly used to assess clubfoot severity; both assign a numerical score based on the degree of each anatomic factor to rate the degree of deformity. Classification of the severity does not seem to correlate well with prognosis but can aid clinicians in tracking the progress of clubfoot correction and in monitoring for recurrence [23, 24].

Radiographic Studies/Testing/Evaluation

With the advancement of prenatal ultrasound, clubfoot can often be diagnosed before birth. The most accurate time for prenatal diagnosis is the 20–24 week ultrasound during the second trimester [25, 26]. The false positive rate has been reported to be up to 40% but recently with improvements, is 10–20% with less false positives at specialized centers. Specificity is higher when bilateral clubfoot is identified. Clubfoot identified on prenatal US can be isolated or complex if associated with other anomalies. Many pediatric orthopedists will offer prenatal counseling to manage expectant families concerns.

Radiographs are not required for initial clubfoot management, however can be utilized to assess ankle dorsiflexion, follow patients long term and to assess the structure of the ankle in children with a history of prior surgical intervention. Anterior posterior (AP) and lateral foot radiographs typically show a decreased in the talocalcaneal angle in both views and ankle equinus with "parallelism" of the talus and calcaneus (Fig. 5.2a and b).

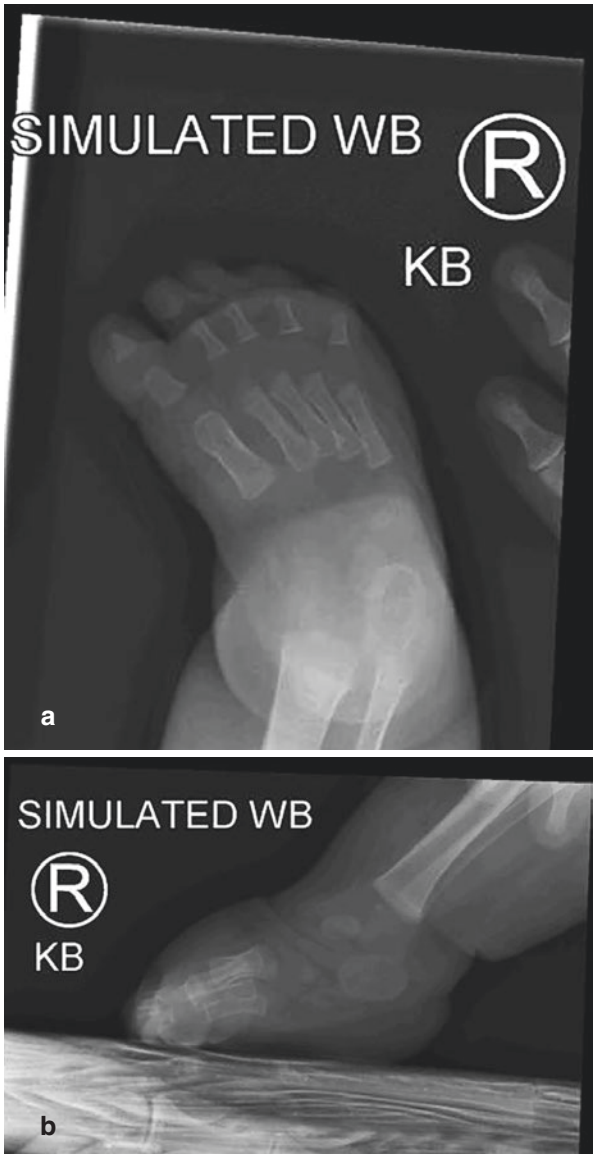


Fig. 5.2 (**a**) AP unilateral clubfoot. (**b**) Lateral unilateral clubfoot

Treatment/Management

The Ponseti method of serial manipulation and casting has become the standard of care. Historically, the pendulum for addressing clubfoot has gone from serial manipulations to extensive surgeries back to serial casting and manipulation. Dr. Ponseti's techniques gain wide acceptance in the late 1990s and early 2000s. Dr. Ponseti wrote that his goal was not to "attain a perfect anatomical result" but to

obtain a "functional, pain free, plantigrade foot with mobility, without calluosities, that does not necessitate the wearing of modified shoes" [27].

The Ponseti method consists of a minimally invasive approach with a correction and maintenance phase. During the "correction phase," weekly long leg casts are applied to the infant that is changed every 5–7 days. On average, correction is achieved with 5–6 casts. Traditionally, plaster material has been used but many clubfoot centers use soft cast material with comparable results [28, 29] (Fig. 5.3a and b). The C-A-V-E mnemonic is useful not only to remember the elements of the deformity but also represent the order of correction using the Ponseti technique. The cavus, adductus, and varus are corrected simultaneously through casting while the remaining equinus is the last to be corrected by performing a percutaneous Achilles tenotomy (Fig. 5.3c and d). Tenotomy surgery is a minor procedure that can be done in the clinic, operating room, or sedation suite based on institutional practice required for 70–90% of patients (Video 5.1). After the tenotomy procedure, patients are placed in a final long leg cast in maximal dorsiflexion and forefoot abduction for 3 weeks (Figs. 5.3e–g and 5.4). This is followed by the maintenance period of bracing with a foot abduction orthosis worn full time initially for 3 months and then transitioned to nighttime and nap part time wear until around age 4 (Fig. 5.5). Children with TEV are monitored carefully for recurrence or relapse. If there is an early relapse, the initial intervention is to resume casting and depending on correction obtained with non-operative means, may require additional surgery (Fig. 5.5). Brace adherence can be a challenge with families and brace wear nonadherence is a major risk factor for recurrence.

Goldstein et al. demonstrated that patients with brace nonadherence were eight times more likely to need surgery [30]. The reported nonadherence rate is 30–49% [31]. Compliance monitor studies have found that there is a significant difference between parent self-report compared to actual time in brace with a pressure sensor [32]. These studies underscore the importance of more research on how to promote brace adherence.

Treatment for TEV typically begins in early infancy. Historically, many providers recommended treatment immediately after birth. However, there does not appear to be an advantage to starting treatment early in the neonatal period. Children with treatment initiated after 4 weeks may have decreased risk of casts slipping/shifting position [33]. Beginning treatment between 2 and 6 weeks of life allows children to complete casting and full-time bracing by about 7 months. Delaying treatment initiation beyond 3–4 months may lead to increased risk of gross motor delays as bracing can interfere with ability to crawl, cruise, and walk.

Fig. 5.3 (**a**) Clinical progression in plaster casts to final correction. Courtesy of Matthew A. Halanski, MD. (**b**) Example of soft cast fiberglass material for Ponseti casting. (**c**) Clinical progression of plantar foot from initial presentation to final correction (**d**) Clinical progression of lateral ankle showing initial plantarflexion contracture to normal dorsiflexion of ankle after tenotomy. (**e** and **f**) Heel Cord Achilles Tenotomy procedure and post tenotomy dorsiflexion. Used with permission of the Children's Orthopaedic Center, Los Angeles. (**g**) Healed Achilles tendon 2 years after the heel cord tenotomy. Courtesy of Ken J. Noonan, MD

Fig. 5.3 (continued)

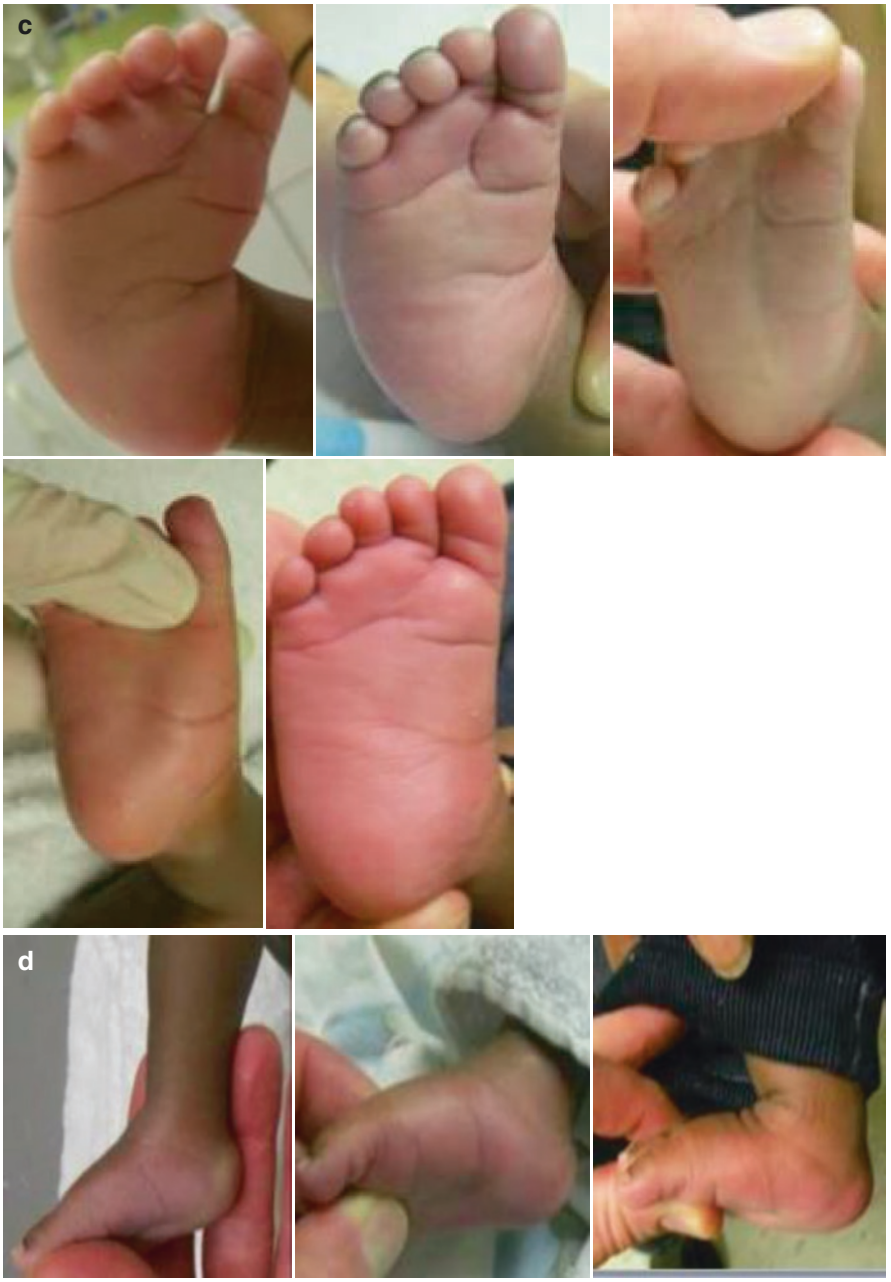


Fig. 5.3 (continued)

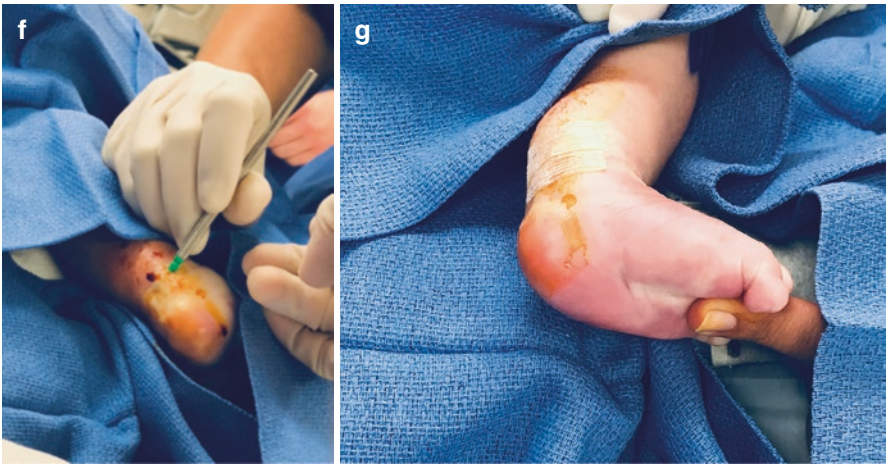


Fig. 5.3 (continued)

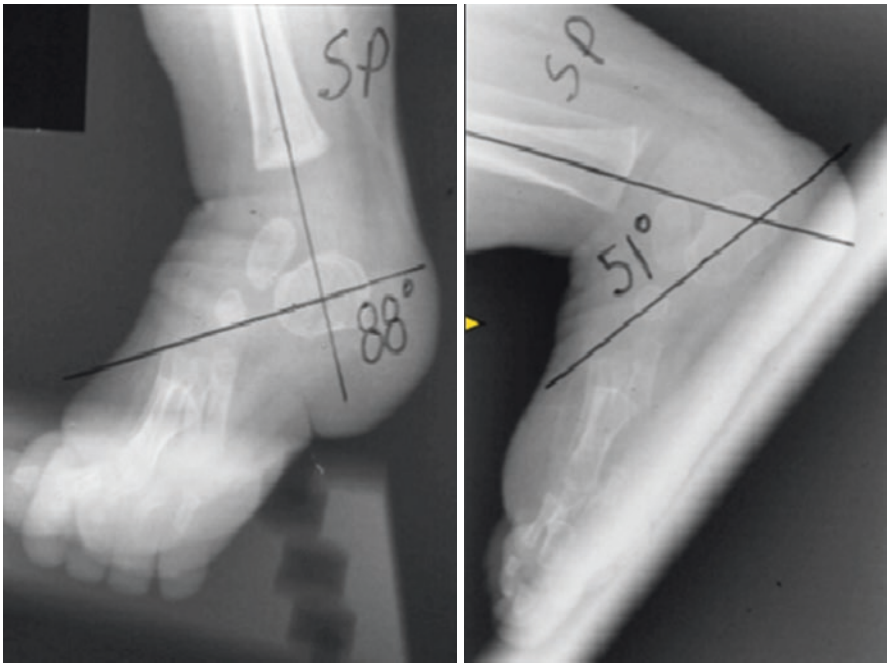


Fig. 5.4 Improvement in tibiocalcaneal angle after tenotomy. Courtesy of Ken J. Noonan, MD

Fig. 5.5 Example of one type of foot abduction orthosis—Mitchell Ponseti Foot Abduction Orthosis in a patient with unilateral right clubfoot after correction. Note the forefoot is maximally abducted to 70° while the unaffected left foot is at 40°

Children who undergo Ponseti casting for idiopathic clubfoot typically achieve gross motor milestones in the normal to late-normal range. Sala et al. reported in their study that children who presented with moderate deformity started walking at an average of 14.2 months while those with severe deformity or relapse walked at an average age of 16 months [34].

The French functional method is another non-surgical technique for clubfoot correction. The French method consists of daily physical therapy for stretching and taping, use of a continuous passive movement device, and nighttime splints. This method is expensive and labor intensive and places high demands on families [35].

Natural History, Primary and Secondary Prevention

Individuals with untreated TEV are unable to ambulate normally and typically report pain and have functional limitations (Fig. 5.6a and b). The majority of children who present for initial clubfoot treatment after 1–2 years of age have good outcomes. However, older children typically require more casts and have higher rates of subsequent surgery. Early recognition of clubfoot with prompt treatment before the age of 6 months yields the best results [36–38] (Fig. 5.7).

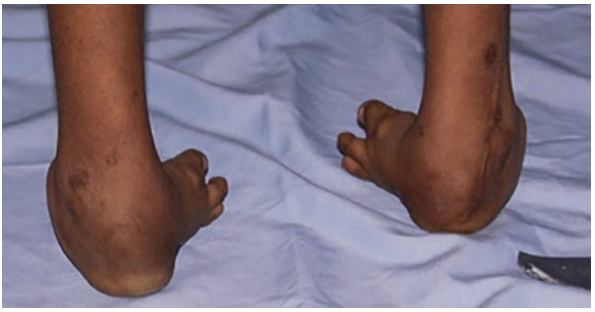


Fig. 5.6 8-year-old twins with neglected clubfoot. Courtesy of Ken J. Noonan, MD

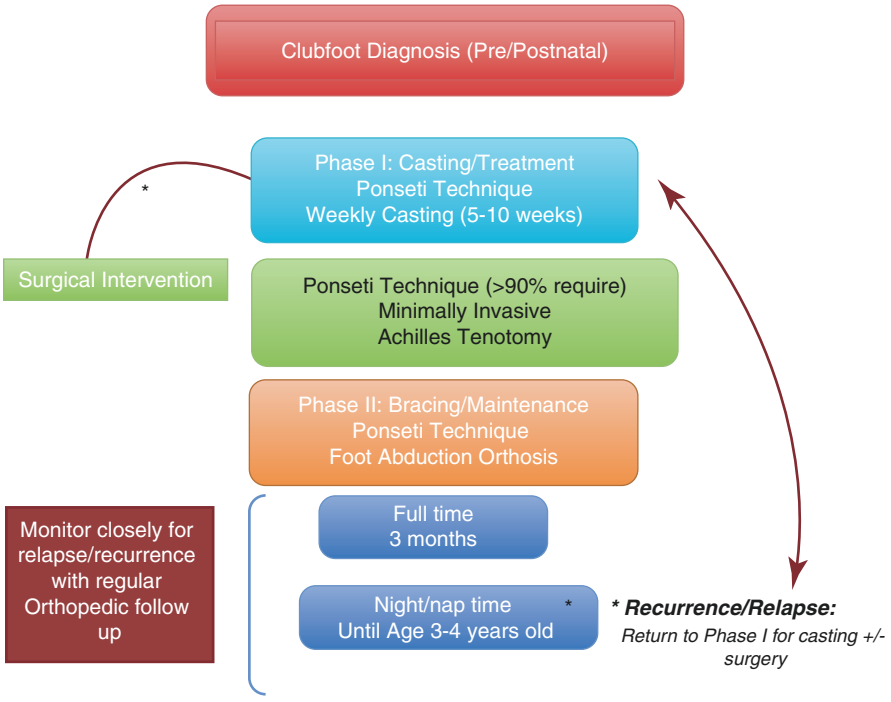


Fig. 5.7 Clubfoot journey of treatment, Courtesy of Melissa A. Bent, MD

References

1. Wynne-Davies R. Family studies and aetiology of club foot. J Med Genet. 1965;2(4):227–32.
2. Smythe T, Kuper H, Macleod D, Foster A, Lavy C. Birth prevalence of congenital talipes equinovarus in low- and middle-income countries: a systematic review and meta-analysis. Tropical Med Int Health. 2017;22(3):269–85.
3. Dietz FR, Cole WG, Tosi LL, et al. A search for the gene(s) predisposing to idiopathic clubfoot. Clin Genet. 2005;67(4):361–2.
4. Cartlidge IJ. Club foot in the Polynesian: an epidemiological survey. N Z Med J. 1983;96(735):515–7.
5. Yang HY, Chung CS, Nemechek RW. A genetic analysis of clubfoot in Hawaii. Genet Epidemiol. 1987;4(4):299–306.
6. Dobbs MB, Gurnett CA. Genetics of clubfoot. J Pediatr Orthop B. 2012;21(1):7–9.
7. Wynne-Davies R. Genetic and environmental factors in the etiology of talipes equinovarus. Clin Orthop Relat Res. 1972;84:9–13.
8. Engell V, Damborg F, Andersen M, Kyvik KO, Thomsen K. Club foot: a twin study. J Bone Joint Surg Br. 2006;88(3):374–6.
9. Ponseti IV. Congenital clubfoot: fundamentals of treatment. New York: Oxford University Press; 1996.
10. Wynne-Davies R. Talipes equinovarus: a review of eighty-four cases after completion of treatment. J Bone Joint Surg Br. 1964;46:464–76.
11. Ippolito E, Ponseti IV. Congenital club foot in the human fetus. A histological study. J Bone Joint Surg Am. 1980;62(1):8–22.
12. Hootnick DR, Levinsohn EM, Crider RJ, Packard DS. Congenital arterial malformations associated with clubfoot. A report of two cases. Clin Orthop Relat Res. 1982;167:160–3.
13. Merrill LJ, Gurnett CA, Siegel M, Sonavane S, Dobbs MB. Vascular abnormalities correlate with decreased soft tissue volumes in idiopathic clubfoot. Clin Orthop Relat Res. 2011;469(5):1442–9.
14. Honein MA, Paulozzi LJ, Moore CA. Family history, maternal smoking, and clubfoot: an indication of a gene-environment interaction. Am J Epidemiol. 2000;152(7):658–65.
15. Wang JH, Palmer RM, Chung CS. The role of major gene in clubfoot. Am J Hum Genet. 1988;42(5):772–6.
16. Alvarado DM, Aferol H, McCall K, et al. Familial isolated clubfoot is associated with recurrent chromosome 17q23.1q23.2 microduplications containing TBX4. Am J Hum Genet. 2010;87(1):154–60.
17. Weymouth KS, Blanton SH, Powell T, Patel CV, Savill SA, Hecht JT. Functional assessment of clubfoot associated HOXA9, TPM1, and TPM2 variants suggests a potential gene regulation mechanism. Clin Orthop Relat Res. 2016;474(7):1726–35.
18. Little DG, Aiona MD. Limb length discrepancy in congenital talipes equinovarus. Aust N Z J Surg. 1995;65(6):409–11.
19. Shimode K, Miyagi N, Majima T, Yasuda K, Minami A. Limb length and girth discrepancy of unilateral congenital clubfeet. J Pediatr Orthop B. 2005;14(4):280–4.
20. Isaacs H, Handelsman JE, Badenhorst M, Pickering A. The muscles in club foot—a histological histochemical and electron microscopic study. J Bone Joint Surg Br. 1977;59-B(4):465–72.
21. Mahan ST, Yazdy MM, Kasser JR, Werler MM. Is it worthwhile to routinely ultrasound screen children with idiopathic clubfoot for hip dysplasia? J Pediatr Orthop. 2013;33(8):847–51.
22. Paton RW, Choudry QA, Jugdey R, Hughes S. Is congenital talipes equinovarus a risk factor for pathological dysplasia of the hip?: a 21-year prospective, longitudinal observational study. Bone Joint J. 2014;96-B(11):1553–5.
23. Flynn JM, Donohoe M, Mackenzie WG. An independent assessment of two clubfoot-classification systems. J Pediatr Orthop. 1998;18(3):323–7.
24. Diméglio A, Bensahel H, Souchet P, Mazeau P, Bonnet F. Classification of clubfoot. J Pediatr Orthop B. 1995;4(2):129–36.

25. Sharon-Weiner M, Sukenik-Halevy R, Tepper R, Fishman A, Biron-Shental T, Markovitch O. Diagnostic accuracy, work-up, and outcomes of pregnancies with clubfoot detected by prenatal sonography. Prenat Diagn. 2017;37(8):754–63.
26. Faldini C, Fenga D, Sanzarello I, Nanni M, Traina F, Rosa MAA. Prenatal diagnosis of clubfoot: a review of current available methodology. Folia Med (Plovdiv). 2017;59(3):247–53.
27. Ponseti IV. Treatment of congenital club foot. J Bone Joint Surg Am. 1992;74(3):448–54.
28. Zmurko MG, Belkoff SM, Herzenberg JE. Mechanical evaluation of a soft cast material. Orthopedics. 1997;20(8):693–8.
29. Coss HS, Hennrikus WL. Parent satisfaction comparing two bandage materials used during serial casting in infants. Foot Ankle Int. 1996;17(8):483–6.
30. Goldstein RY, Seehausen DA, Chu A, Sala DA, Lehman WB. Predicting the need for surgical intervention in patients with idiopathic clubfoot. J Pediatr Orthop. 2015;35(4):395–402.
31. Dobbs MB, Rudzki JR, Purcell DB, Walton T, Porter KR, Gurnett CA. Factors predictive of outcome after use of the Ponseti method for the treatment of idiopathic clubfeet. J Bone Joint Surg Am. 2004;86(1):22–7.
32. Zionts LE, Dietz FR. Bracing following correction of idiopathic clubfoot using the Ponseti method. J Am Acad Orthop Surg. 2010;18(8):486–93.
33. Zionts LE, Sangiorgio SN, Cooper SD, Ebramzadeh E. Does clubfoot treatment need to begin as soon as possible? J Pediatr Orthop. 2016;36(6):558–64.
34. Sala DA, Chu A, Lehman WB, van Bosse HJ. Achievement of gross motor milestones in children with idiopathic clubfoot treated with the Ponseti method. J Pediatr Orthop. 2013;33(1):55–8.
35. Noonan KJ, Richards BS. Nonsurgical management of idiopathic clubfoot. J Am Acad Orthop Surg. 2003;11(6):392–402.
36. Adegbehingbe OO, Adetiloye AJ, Adewole L, et al. Ponseti method treatment of neglected idiopathic clubfoot: preliminary results of a multi-center study in Nigeria. World J Orthop. 2017;8(8):624–30.
37. Ayana B, Klungsøyr PJ. Good results after Ponseti treatment for neglected congenital clubfoot in Ethiopia. A prospective study of 22 children (32 feet) from 2 to 10 years of age. Acta Orthop. 2014;85(6):641–5.
38. Digge V, Desai J, Das S. Expanded age indication for Ponseti method for correction of congenital idiopathic talipes equinovarus: a systematic review. J Foot Ankle Surg. 2018;57(1):155–8.

Chapter 6
Congenital Vertical Talus

Ayesha Maqsood

The goal of this chapter is to outline a rare deformity of the pediatric foot: congenital vertical talus (CVT).

Brief Overview of Condition

Congenital vertical talus (CVT) is an uncommon foot deformity that presents at birth. The condition can be idiopathic, but in most cases is associated with a neuromuscular disease or a genetic syndrome [1]. It appears most commonly as a rigid, flat foot with a convex sole, or rocker-bottom appearance. This is due to the dorsal dislocation of the medial column of the foot at the talonavicular joint, or of the entire midfoot on the hindfoot [1]. Lateral radiographs of the foot in neutral and maximum plantar flexion are diagnostic and will determine whether the dislocation can be reduced [1]. CVT does not resolve spontaneously, therefore medical intervention is required. Due to the rigid nature of the deformity, many patients have historically required extensive soft-tissue release surgery. However, a new, less invasive technique involving serial manipulations and casting with a percutaneous release of the Achilles tendon has been shown to lead to successful outcomes [1].

A. Maqsood (✉)
Department of Surgery, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA
e-mail: amaqsood@luriechildrens.org

J. F. Sarwark, R. L. Carl (eds.), *Orthopaedics for the Newborn and Young Child*,
https://doi.org/10.1007/978-3-031-11136-5_6

Background Including Epidemiology and Pathoanatomy

Congenital vertical talus has an estimated prevalence of 1 in 10,000 live births [2]. This number may be low as mild cases are likely to be missed in the newborn period. Given the low prevalence of this condition, there is very little data available about demographic factors that increase the risk of CVT [2].

The etiology of CVT is currently unknown but the deformity has been frequently associated with a wide variety of other disorders. Ogata et al. proposed a CVT classification system that divides patients into the following groups: genetic/syndromic, neuromuscular, and idiopathic [3]. The most common defects and disorders associated with CVT include trisomy 13, 18 [4], arthrogryposis, and myelomeningocele [5]. In about 20% of idiopathic cases, affected individuals have a positive family history with the deformity inherited in an autosomal dominant fashion [6]. Researchers are also working to identify the genes involved and some were identified as causative. Ultimately, there is not a single gene theory that explains all cases of CVT, supporting the idea that the etiology of CVT may be heterogeneous in nature.

The pathoanatomy of CVT consists of a rigid foot deformity and soft-tissue contractures. The foot deformity is an irreducible dorsolateral navicular dislocation with a vertically oriented talus and a calcaneal eversion with attenuated spring ligament [7]. The talar head and neck are in an abnormal shape and orientation, essentially stretching and weakening the plantar soft tissues, giving way to the rocker-bottom appearance of the foot [2]. Also since the posterior tibial tendon and the peroneus longs and brevis are commonly subluxated over the medial and later malleolus; they function more as ankle dorsiflexers rather than plantar flexors [8].

Clinical Presentation: History and Physical

One of the more notable clinical characteristic of CVT is the curved plantar surface of the foot. The newborn's forefoot and midfoot in dorsiflexion and the hindfoot in plantar flexion and valgus lead to the classic rocker-bottom appearance. This can be apparent at birth or when the child begins to walk. The abnormal position of the foot will cause the child to walk on the inside of their foot, while the outside edge is elevated, leading to improper balance and weight distribution [9].

There are other, milder deformities that can be confused with CVT, such as calcaneovalgus foot and oblique talus. Some key distinguishing features for CVT are the rigidity of the deformity and the presence of the hindfoot equinus. The forefoot and midfoot dorsiflexion cause deep creases on the dorsal aspect of the foot. The extreme forefoot dorsiflexion also creates a distinct dorsal palpable gap, where the navicular and talar head would articulate in a normal foot [2]. The examination of

this gap can help the physician assess for rigidity of the deformity. In a CVT foot, the gap would remain when the foot is plantar flexed, but would disappear in a calcaneovalgus foot [8]. Physicians need to distinguish between CVT, calcaneovalgus, and oblique talus because CVT requires early intervention with casting and surgery, while the other two conditions can be treated conservatively with observation and/or casting and stretching.

Since CVT has frequently been associated with neuromuscular and genetic abnormalities, a comprehensive physical examination should be completed. The physician should observe for any dysmorphic features that would merit referral to a geneticist, or any signs of neurologic or neuromuscular conditions that would indicate the need to refer a child to neurology, neurosurgery, or for magnetic resonance imaging (MRI) evaluation of the spine [2]. Another important part of the physical examination is the serial documentation of motor function of the foot and ankle, giving special attention to the toe flexors and extensors [2]. This is done by separately stimulating the plantar and dorsal aspects of the child's foot in order to elicit plantar flexion and dorsiflexion of the toes. Miller et al. noted that a level of absent or slight ability to move the toes with stimulation correlates with a congenital vertical talus deformity that is more rigid and less responsive to treatment [2].

Evaluation

Early detection of this deformity is important for successful treatment. A comprehensive medical history and physical examination of the child should be performed. Since CVT can be associated with neuromuscular disease or genetic syndromes, the physician may decide to perform additional tests to determine whether the child has any associated conditions [9]. In order to have a better understanding of the anatomy of the child's foot, the physician should order foot radiographs. The recommended imaging studies include radiograph views of weight bearing AP (if the child is old enough; neutral position for infants) and lateral forced plantarflexion views of the fee to confirm diagnosis [10].

There are a few radiographic findings typical of CVT: the long axis of the talus is vertical, positioned parallel to the longitudinal axis of the tibia on the lateral view, the calcaneus is in significant equinus, and the talocalcaneal angle is increased [8]. In order to assess the rigidity of the deformity and differentiate between a diagnosis of CVT and milder conditions, forced plantar flexion and dorsiflexion lateral radiographs are required. With CVT, forced plantar flexion radiographs show persistent malalignment of the long axis of the talus and the first metatarsal (Fig. 6.1), while forced dorsiflexion lateral radiographs demonstrate persistently decreased tibiocalcaneal angles indicating fixed hindfoot equinus [8]. In contrast, a forced plantar flexion lateral radiograph in a patient with oblique talus will demonstrate restoration

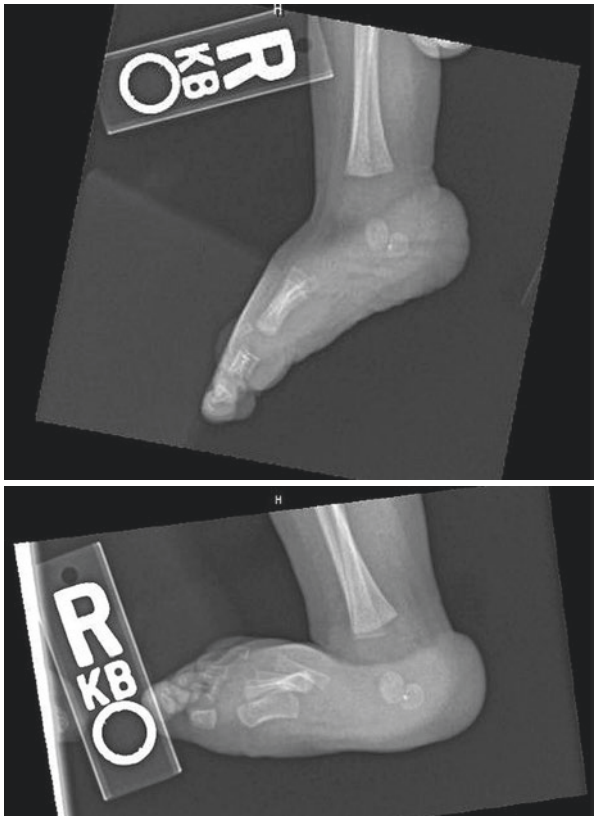


Fig. 6.1 In these lateral foot X-rays, even with the infant's foot in forced plantarflexion, the talus remains in a vertical position rather than aligning with the metatarsals. Images courtesy of Rebecca L. Carl, MD

of a normal relationship between the long axis of the talus and the first metatarsal [8]. Also on the lateral view, Hamanishi described two radiographic angles, the talar axis-first metatarsal base angle (TAMBA) and the calcaneal axis-first metatarsal base angle (CAMBA) [11]. The TAMBA describes how the talus lines up with first metatarsal. They described the changing point from a flexible oblique talus to a rigid CVT as a TAMBA of approximately 60° and a CAMBA of 20° [11].

The diagnosis of CVT can be difficult due to the cartilaginous nature of the bones in a newborn's foot. The talus, tibia, calcaneus, and metatarsals are ossified at birth, whereas the cuboid ossifies during the first month of life, the cuneiforms at 2 years of age and the navicular at 3 years of age [8]. Most children with suspected CVT are seen in the newborn stage, which is why the diagnosis of CVT is established by the relationships between the ossified structures on radiographic evaluation.

Orthopedic providers should consider obtaining an MRI of the spine to evaluate for spinal cord abnormalities (e.g., tethered cord, syrinx) for children with signs of central or peripheral neuropathy [9].

Management

True congenital vertical talus does not resolve spontaneously; some form of treatment will be required. If left untreated, the foot position will worsen, especially with weight bearing. When treating CVT, the goal is to provide the child with a stable, pain free foot that is also functional. The earlier the deformity is treated, the better the outcome will be. Historically, the main form of treatment was an extensive surgical approach that could lead to future complications such as stiffness and arthritis. Now, the Dobbs technique, which involves placing a series of casts with careful molding, followed by minimally invasive surgery, has provided another, less invasive option for treatment.

Physicians may sometimes start with a non-surgical treatment to prevent the deformity from worsening by increasing the flexibility of the foot. This approach includes stretching exercises for the forefoot and hindfoot and serial manipulation and casting of the forefoot and midfoot in a flexed position to reduce the upward curve of the foot [9]. However, improvements from this treatment are generally temporary.

In a traditional surgical approach, the type of procedure used is based on the age of the patient, the severity of the deformity, and preference of the surgeon [8]. Up to the age of 3 years, children are usually offered an open reduction of the talonavicular joint, which can be performed in either a one-stage or two-stage procedure [8]. The one-stage procedure is the preference of most orthopedic surgeons because it has fewer complications, such as avascular necrosis, as compared to the two-stage procedure. The main components of the surgical approach consist of a reduction of the talonavicular joint held by a Kirschner wire placed across the joint, lengthening of the toe extensor and peroneal to improve ankle plantarflexion and forefoot adduction and correction of the ankle equinus contracture by lengthening the Achilles tendon and releasing the ankle and subtalar joint capsules [8]. Though surgery can dramatically improve a child's outcome, the open reduction approach is associated with significant short-term (wound necrosis, undercorrection, stiffness of ankle and subtalar joint, and need for triple arthrodesis) and long-term (degenerative arthritis) complications [8].

Another treatment option is the Dobbs technique, which consists of serial manipulation and cast immobilization based on the principles of the Ponseti method used for clubfoot deformity, followed by pinning of the talonavicular joint and percutaneous tenotomy of the Achilles tendon [12]. The treatment starts with about 6 weekly manipulations, with stretching the foot in plantar flexion and inversion with the one hand while counter pressure is applied with the thumb with the opposite hand to the medial aspect of the head of the talus [8]. The aim is to adequately stretch the contracted tendons and soft tissues by pushing the anterior aspect of the talus superiorly and laterally and pulling the forefoot medially and into

plantarflexion. Next, a series of four to six long-leg plaster casts are applied to hold the foot in the desired amount of correction [8], so the talonavicular joint is properly reduced. A lateral foot radiograph is then taken in the cast to ensure reduction is achieved. This is confirmed indirectly by the TAMBA, by ensuring that the first metatarsal bones line up with the talus, as the navicular is not yet ossified in infants [8]. Once the radiograph shows evidence of a successful reduction, the patient is scheduled for a minimally invasive surgery for a percutaneous Achilles tendon tenotomy to the fix the residual equinus deformity and then fixation of the talonavicular joint via a Kirschner wire [8]. Post-operatively, a series of long-leg casts are applied to maintain the position of the foot and ankle. The first cast with the foot in neutral and the ankle in 5° of dorsiflexion, the next with the ankle in 10°–15° of dorsiflexion for 3 weeks and finally with the ankle in neutral for an additional 3 weeks [8]. Lastly, in order to prevent reoccurrences, children wear a night-time brace, which consists of two shoes connected with a bar. The brace is typically worn full time for 2 months and then at nighttime until the age of 2 [13]. Patients should be seen regularly from the time the brace is started until skeletal maturity is reached. This approach has provided excellent results in terms of clinical appearance of the foot, deformity correction, and foot function as measured radiographically at 2 years in patients with CVT [12].

Natural History, Primary and Secondary Prevention

Congenital vertical talus is a rare pedal deformity recognizable at birth by a dislocation of the talonavicular joint, resulting in a characteristic radiographic near-vertical orientation of the talus and rocker-bottom feet appearance. It can occur both unilaterally and bilaterally. If left untreated, the condition will worsen due to secondary adaptive changes occurring in the tarsal bone as a result of weight bearing [2]. For example, callosities can develop along the plantar medial border of the foot; around the unreduced talar head, pain develops [2], the child's gait is affected, and the ability to wear properly fitting shoes becomes difficult [13].

Though the etiology of CVT is unknown, it is believed to be idiopathic or associated with genetic syndromes or neuromuscular disorders. Therefore, currently the prevention of congenital vertical talus is not possible [13].

References

1. Sarwark JF, editor. Essentials of musculoskeletal care. 4th ed. Rosemont, IL: American Academy of Orthopaedic Surgeons; 2010. p. 144–1045.
2. Miller M, Dobbs MB. Congenital vertical talus: etiology and management. J Am Acad Orthop Surg. 2015;23(10):604–11.
3. Ogata K, Schoenecker PL, Sheridan J. Congenital vertical talus and its familial occurrence: an analysis of 36 patients. Clin Orthop Relat Res. 1979;139:128–32.3.

4. Townes PL, Manning JA, Dehart GK Jr. Trisomy 18 associated with congenital glaucoma and optic atrophy. J Pediatr. 1962;61:755–8.
5. Sharrard WJ, Grosfield I. The management of deformity and paralysis in the foot in myelomeningocele. J Bone Joint Surg Br. 1968;50(3):456–65.
6. Dobbs MB, Gurnett CA, Pierce B, et al. HOXD10 M319K mutation in a family with isolated congenital vertical talus. J Orthop Res. 2006;24(3):448–53.
7. Children's Hospital of Philadelphia. Congenital vertical talus. 2019. https://www.chop.edu/conditions-diseases/congenital-vertical-talus. Accessed 7 Feb 2019.
8. Alaee F, Bohem S, Dobbs MB. A new approach to the treatment of congenital vertical talus. J Child Orthop. 2007;1(3):165–74.
9. Ortho Bullets. Congenital vertical talus. 2019. https://www.orthobullets.com/pediatrics/4066/congenital-vertical-talus. Accessed 4 Feb 2019.
10. Thomson JD. Congenital vertical talus. 2019. https://emedicine.medscape.com/article/1259681-workup. Accessed 7 Feb 2019.
11. Hamanishi C. Congenital vertical talus: classification with 69 cases and new measurement system. J Pediatr Orthop. 1984;4(3):318–26.
12. Dobbs MB, Purcell DB, Nunley R, Morcuende JA. Early results of a new method of treatment for idiopathic congenital vertical talus. J Bone Joint Surg Am. 2006;88(6):1192–200.
13. Children's Hospital St. Louis. Vertical talus. 2019. https://www.stlouischildrens.org/conditions-treatments/center-foot-disorders/vertical-talus. Accessed 4 Feb 2019.

Chapter 7
Congenital Curly Toe Contractures

Peter R. Swiatek

Background

Curly toe is a common congenital flexion deformity of the proximal interphalangeal (PIP) joint most typically involving the third, fourth, and fifth toes of affected pediatric patients [1]. Associated medial deviation or varus deformity of the flexed "curly toe" often causes overriding of adjacent toes. Although curly toe is typically asymptomatic in children and usually resolves in 20–25% of cases [2], the deformity often causes concern among parents and may lead to pressure-related symptoms, including nail deformities, in adolescence and into adulthood. Management of curly toe in the pediatric patient ranges from watchful waiting and taping to operative flexor tendon tenotomies and flexor to extensor tendon transfers. The purpose of this chapter is to review the clinical presentation of curly toe deformity, the relevant anatomy, and the options for operative versus non-operative intervention.

Clinical Presentation

Curly toe is typically recognized in neonates and infants by the classic flexion and varus deformity in at least one of the lateral three toes (see Fig. 7.1), and many affected patients will have bilateral and symmetric curly toe deformities [3]. Patients with a curly deformity of the second toe will typically have a valgus deformity with an overriding third toe [4]. Passive motion of the curly toe should allow full extension and correction of varus deformity. Passive dorsiflexion at the ankle should cause exaggeration of the deformity. Curly toe is not painful and not associated with neurovascular abnormalities. The etiology of curly toe is unknown but thought to

P. R. Swiatek (✉)
Department of Orthopaedic Surgery, Northwestern Memorial Hospital, Chicago, IL, USA
e-mail: Peter.swiatek@northwestern.edu

J. F. Sarwark, R. L. Carl (eds.), *Orthopaedics for the Newborn and Young Child*,
https://doi.org/10.1007/978-3-031-11136-5_7

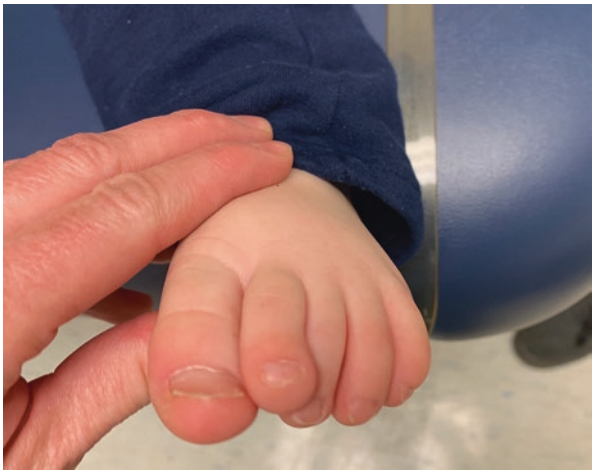


Fig. 7.1 Case of left foot curly toes. Curly toe deformity of the lateral toes causing the classic "curling" of the third toe under the second toe. Image courtesy of Rebecca L. Carl, MD

have a strong genetic component. A thorough family history is likely to reveal parents or siblings with similar curly toe deformity.

Testing and Evaluation

Diagnosis of curly toe deformity is almost entirely clinical. Radiographs, laboratory studies, and neurological evaluation may be useful for ruling out other conditions associated with pediatric foot abnormalities, including trauma, inflammation, neuromuscular disorders that cause lower extremity weakness and compensatory flexion of the toes. Additionally, radiographs may be helpful for pre-operative surgical planning.

Treatment

Non-operative Management

Non-operative treatment involves watchful waiting, passive stretching, and "strapping" of the affected toe. Watchful waiting is recommended for mild deformities in infants and toddlers with full resolution for deformity in up to a quarter of those affected. The effectiveness of passive stretching of the toes has not been well-studied, however there is little downside to having parents learn a home stretching program. "Strapping" or taping of the toe involves creating a supportive hammock under the affected curly toe with the intention of passively correcting the deformity over time. Despite the common use of strapping, the literature suggests that these

modalities are unlikely to affect the natural history of the deformity [2]. For example, a retrospective review of 24 children and 44 toes demonstrated a 68% improvement in symptoms with strapping but a significant loss of correction with cessation of treatment [4]. Authors of the study recommend treatment only for moderate to severe toe deformities; and for these cases, the authors recommend operative management.

Operative Management

Three operative approaches to treatment of moderate to severe curly toe have been described and studied. Surgery is typically recommended for symptomatic curly toe deformity in patients aged three to six and older. Techniques include (a) open tenotomy of both slips of the flexor digitorum brevis (FDB) and flexor digitorum longus (FDL), (b) open tenotomy of one slip of the flexor digitorum brevis (FDB) tendon only, and (c) transfer of the FDL to the extensor hood of the affected toe.

Open Tenotomy of FDB Tendon Slip

Similar to surgical treatment of camptodactyly of the hand, open tenotomy of the FDB with dissection of the collateral ligament, volar plate, and reconstruction of the plantar defect is described by Tokioka et al. [5]. Like the surgical approach for camptodactyly, open tenotomy is directed at correcting flexion deformity caused by an imbalance of extension and flexion forces, such as the tight FDB or overlying ligamentous tissues.

An incision is made on medial side of the affected toe, extending proximal to the plantar crease of the toe. Dissection is made through subcutaneous tissue, and the neurovascular bundle is identified. The tendon sheath of FDB is incised, revealing the FDB tendon and the medial slip of FDB. The medial slip is released, and the toe is tested in flexion and extension for adequate correction. For further correction, the collateral ligament and volar plate at the proximal interphalangeal joint can be dissected. The resulting skin defect can be closed with a local skin graft, such as a plantar flap on the web of affected toes, or with a full-thickness skin graft, such as from the ankle [5]. Tokioka et al. described their success performing this procedure in a case series of eight toes in seven patients with a median age of two-and-one-half years. They found overlapping flexion and varus deformity correction without complication in all seven patients, with only mild residual flexion varus deformity remaining for only the most severe cases of curly toe. They reported no functional impairment of affected toes, owing this outcome to preservation of both the FDL and FDB tendons. Based upon these results, the authors recommended open tenotomy of one slip of the FDB in moderate to severe cases of children younger than 3 years old and observation in cases of mild deformity. For surgical cases, they recommend intervention early to avoid the sequelae of prolonged muscle

imbalance, such as skeletal and cartilaginous deformity, which cannot be corrected with this procedure [5].

Open Tenotomy of FDB and FDL Tendon Slips

Similar to the aforementioned approach in open tenotomy of the FDB slip, the approach to the FDB and FDL can start with a longitudinal incision distal to the proximal plantar crease or with a transverse incision, recommended by Ross et al. In this transverse approach, an incision is made just distal to the proximal plantar crease. The flexor tendon sheath is divided, the FDB and FDL are elevated through the wound and explored, FDB and FDL slips are excised, and the deformity correction is observed. Additional correction may be achieved by passive manipulation of the surgical toe [6].

In their report of 62 children with hammer toes and/or curly toes, Ross et al. reported a success rate of 95%, with the only failures attributable to extension of scar across one or more flexion creases, resulting in a scar tether. Their sample included children with a median age of nearly 10 years. 64% of children reported good or normal results and 31% reported only mild residual deformity. The authors conclude that open FDL and FDB tenotomy is an effective method for treatment of curly toe deformity given that there is no other suspected etiology beyond shortened flexor tendons. Moreover, they support open flexor tenotomy over flexor-extensor transfer [6].

Transfer of FDL to Extensor Hood

First described by Taylor et al. in 1951, the flexor-to-extensor tendon transfer was the primary surgical treatment method for curly toe deformity. Approach is similar to open tenotomy. After the FDL is tenotomized, it is sutured to the extensor hood with the rationale that a shortened flexor tendon would assist in extension of the previously hyperflexed digit. In their study comparing 56 toes on 20 children who underwent flexor tenotomy and 63 toes on 16 children who underwent flexor-to-extensor transfer, Pollard and Morrison et al. found that more favorable results in the open tenotomy group. For example, 95% of patients reported fair or good results in the open tenotomy group versus 77% in the flexor-to-extensor transfer group. Moreover, 100% of open tenotomy patients reported fair functional outcomes compared to 34% reporting fair outcomes and 58% reporting poor outcomes in the tendon transfer group, with poor results characterized by stiffness and negligible characterized by stiffness and negligible active or passive movement distal to the metatarsophalangeal joint [7].

References

1. Biyani A, Jones DA, Murray JM. Flexor to extensor tendon transfer for curly toes. 43 children reviewed after 8 (1-25) years. Acta Orthop Scand. 1992;63(4):451–4.
2. Sweetnam R. Congenital curly toes; an investigation into the value of treatment. Lancet. 1958;2(7043):398–400.
3. Sarwark JL, Labella CR. Pediatric orthopaedics and sports injuries: a quick reference guide. Pediatrics AAo, editor. Elk Grove Village, IL; 2014.
4. Turner PL. Strapping of curly toes in children. Aust N Z J Surg. 1987;57(7):467–70.
5. Tokioka K, Nakatsuka T, Tsuji S, Ishida K, Obana K, Osawa K. Surgical correction for curly toe using open tenotomy of flexor digitorum brevis tendon. J Plast Reconstr Aesthet Surg. 2007;60(12):1317–22.
6. Ross ER, Menelaus MB. Open flexor tenotomy for hammer toes and curly toes in childhood. J Bone Joint Surg Br. 1984;66(5):770–1.
7. Pollard JP, Morrison PJ. Flexor tenotomy in the treatment of curly toes. Proc R Soc Med. 1975;68(8):480–1.

Chapter 8
Congenital Dislocation of the Knee (CKD)

Bensen B. Fan

Brief Overview of Condition

Congenital knee dislocation (CKD) refers to a spectrum of knee positions at birth ranging from hyperextension of the knee to full anterior dislocation of the tibia on the femur [1, 2]. It can be either an isolated finding or associated with a syndrome (arthrogryposis, Larsen, myelomeningocele, developmental dysplasia of the hip) [1–5]. Affected infants are typically diagnosed with CKD shortly after birth based on clinical signs of knee hyperextension, transverse anterior skin folds, and a hypoplastic suprapatellar bursa [1, 2]. CKD is commonly associated with other orthopedic conditions including developmental hip dysplasia (50%) and clubfoot (47%); 30% of infants with CKD have a history of breech presentation at birth [1–4]. Treatment ranges from serial casting to surgery depending on the severity of the dislocation. Infants with isolated CKD who receive early treatment typically achieve excellent functional outcomes [4, 6].

Background Including Epidemiology and Pathophysiology

Congenital knee dislocation is estimated to occur 1 in 100,000 infants [7]. Historically, CKD was thought to be due to decreased intra-uterine space and fetal malposition [1]; more recently, physicians have described quadriceps fibrosis with resultant contracture as a contributing factor. There is a polygenic inheritance

B. B. Fan (✉)
Department of Orthopaedic Surgery, Children's Hospital of Los Angeles, Los Angeles, CA, USA

Orlando Health Arnold Palmer Hospital for Children Center for Orthopaedics, Orlando, FL, USA

J. F. Sarwark, R. L. Carl (eds.), *Orthopaedics for the Newborn and Young Child*,
https://doi.org/10.1007/978-3-031-11136-5_8

component similar to developmental dysplasia of the hip (DDH) and clubfoot. The etiology of CKD varies depending on associated syndromes and deformities. However, 30% of congenital knee dislocations are associated with breech presentation, and the deformity can be so severe that, at rest, the feet are level with the head [1–4].

Clinical Presentation: History and Physical

Congenital knee dislocation looks like a hyperextended knee at birth. The tibia is shifted anteriorly relative to the femur. There may be ligamentous laxity and an absent ACL [1, 7], though this may be difficult to assess in an infant with a dislocated knee. Usually, a rotational component at the knee exists and a valgus deformity [1, 7]. There is rarely any neurovascular injury.

CKD is classified into three grades. Grade 1 is a hyperextension, recurvatum deformity. The knee is still located, and on X-ray, the epiphysis of the tibia and femur are in contact. Usually there is greater than 90° of passive flexion. Grade 2 is a subluxation of the knee, with 30–90° of passive flexion. Grade 3 CKD has less than 30° of passive flexion, and is a full dislocation of the knee, in which X-ray will show the tibia fully anterior to the femur [1, 2, 8].

Physical examination should include careful evaluation of the hips given the association between DDH and CKD. Talipes equinovarus (clubfoot) is also commonly associated with CKD. In the setting of bilateral knee dislocations, physicians should look for characteristic features of Larsen syndrome (flat facies, hypertelorism) [5]. In addition to Larsen syndrome, CKD can be seen with arthrogryposis, myelodysplasia, Ehlers-Danlos, and Beals syndrome.

Radiographic Evaluation

While CKD is diagnosed clinically, radiographs of the knee are used to evaluation the position of the tibia relative to the femur and confirm the severity of this condition (Fig. 8.1).

Additionally, hip radiographs, hip ultrasound, and/or a complete skeletal survey may be indicated to assess for associated conditions.

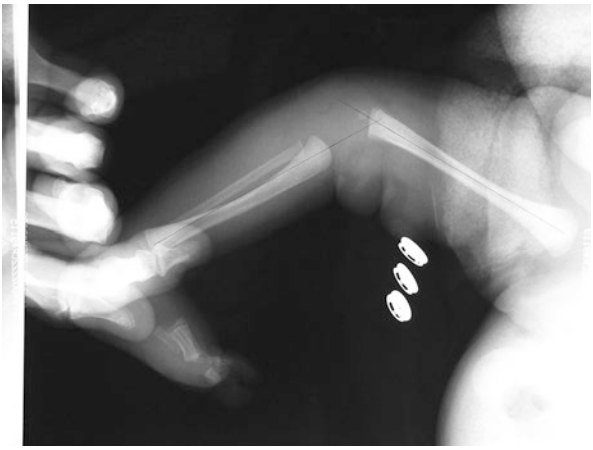


Fig. 8.1 Radiograph of an infant with congenital dislocation of the knee. There is an apex posterior deformity, anterior translation of the tibia relative to the femur, and the knee is hyperextended. Image courtesy of Rebecca L. Carl, MD

Management

Treatment of CKD begins with serial casting and manipulation to increase knee flexion, ideally in the neonatal period [1–4]. The goals of treatment are to obtain 90° of knee flexion. Once knee flexion is obtained, a Pavlik harness can be applied to hold knee(s) is a flexed position. Serial casting is successful in mild CKD with only a recurvatum deformity; however, frank anterior dislocations rarely respond to casting. Failure of serial casting is defined as the inability to gain 30° of flexion after 3 months of casting. Casting should be performed with gentle traction and subsequent flexion to avoid iatrogenic injury, such as plastic deformity of the tibia or femur.

Surgical open reduction of the knee is performed as early as 3 months of age. Surgery is indicated for severe deformities and failure of serial of casting. Usually surgery consists of quadriceps lengthening, and release of the anterior capsule, iliotibial band (IT band), and hamstrings [1, 4]. A femoral shortening osteotomy can be used to aid reduction as well as a substitute for quadriceps lengthening, as some believe a quadriceps lengthening may contribute to an insufficient extensor mechanism, leading to difficulty standing [6, 9]. The goal of surgery is to obtain 90° of flexion and to maintain a stable knee that the patient can stand on. After surgery, patients are casted in 45–60° of knee flexion for 4 weeks.

Clinical Vignettes/Clinical Pearls

Congenital knee dislocation is a spectrum of knee deformity from hyperextension to dislocation. It is often associated with DDH, clubfoot, and syndromes such as arthrogryposis, Larsen syndrome, and myelomeningocele. The anterior cruciate ligament is often absent or attenuated.

Natural History, Primary and Secondary Prevention

Patients with congenital dislocation of the knee in isolation typically have excellent functional outcomes. There are reports of spontaneous resolution in milder cases. In a study of 6 CKD patients treated by observation, 4/6 had residual hyperextension despite "spontaneous reduction" [10]. Early casting is recommended with surgical treatment available for full dislocations and where casting has failed. Even after treatment there can be residual laxity, quadriceps insufficiency, and epiphyseal deformity [2, 11]. Recurrent hyperextension is not common.

The best prognosis is in those children with unilateral CKD that corrects with observation or casting and in those without an associated syndrome [2, 3, 11]. Most patients treated for CKD have functional independent ambulation and can participate in sports. However, some children have difficulty with activities requiring more than 90° of knee flexion (e.g., cycling) [6].

References

1. Niebauer JJ, King DE. Congenital dislocation of the knee. J Bone Joint Surg Am. 1960;42-A:207–25.
2. Curtis BH, Fisher RL. Congenital hyperextension with anterior subluxation of the knee. Surgical treatment and long-term observations. J Bone Joint Surg Am. 1969;51(2):255–69.
3. Johnson E, Audell R, Oppenheim WL. Congenital dislocation of the knee. J Pediatr Orthop. 1987;7(2):194–200.
4. Ko JY, Shih CH, Wenger DR. Congenital dislocation of the knee. J Pediatr Orthop. 1999;19(2):252–9.
5. Larsen LJ, Schottstaedt ER, Bost FC. Multiple congenital dislocations associated with characteristic facial abnormality. J Pediatr. 1950;37(4):574–81.
6. Oetgen ME, Walick KS, Tulchin K, Karol LA, Johnston CE. Functional results after surgical treatment for congenital knee dislocation. J Pediatr Orthop. 2010;30(3):216–23.
7. Jacobsen K, Vopalecky F. Congenital dislocation of the knee. Acta Orthop Scand. 1985;56(1):1–7.
8. Abdelaziz TH, Samir S. Congenital dislocation of the knee: a protocol for management based on degree of knee flexion. J Child Orthop. 2011;5(2):143–9.
9. Johnston CE 2nd. Simultaneous open reduction of ipsilateral congenital dislocation of the hip and knee assisted by femoral diaphyseal shortening. J Pediatr Orthop. 2011;31(7):732–40.

10. Haga N, Nakamura S, Sakaguchi R, Yanagisako Y, Taniguchi K, Iwaya T. Congenital dislocation of the knee reduced spontaneously or with minimal treatment. J Pediatr Orthop. 1997;17(1):59–62.
11. Laurence M. Genu recurvatum congenitum. J Bone Joint Surg Br. 1967;49(1):121–34.

Chapter 9
Fibular Hemimelia/Congenital Short Femur/LLE Deformity

Angielyn San Juan and John J. Grayhack

Introduction

Congenital limb deficiency is a rare clinical entity with well-recognized orthopedic manifestations. The most common fibular hemimelia which is often associated with other anomalies, i.e., congenital short femur [1]. Such deficiencies cover a wide spectrum, ranging from mild hypoplasia to moderate abnormalities in dysplastic limbs, to severe aplasia or complete absence of the involved bone. As such, children will present with varying degrees of limb length discrepancy, abnormalities of femoral morphology at both the hip and knee, knee instability, and associated defects of the tibia and the forefoot [2]. With these associated conditions, management varies significantly depending upon the length and alignment of the limb and the alignment, stability and mobility of the joints. The etiology of these abnormalities remains unclear. While most are sporadic, chromosomal abnormalities, autosomal dominant, autosomal recessive, as well as X-linked transmission have been reported. The overall goal of medical and surgical management is to create or restore functional lower limbs that can achieve weight bearing with a plantigrade foot.

A. S. Juan
Department of Orthopaedics, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA

Northshore University Health System, Skokie, IL, USA
e-mail: asanjuan@northshore.org

J. J. Grayhack (✉)
Baylor College of Medicine, Houston, TX, USA
e-mail: jgrayhack@luriechildrens.org

J. F. Sarwark, R. L. Carl (eds.), *Orthopaedics for the Newborn and Young Child*,
https://doi.org/10.1007/978-3-031-11136-5_9

Background: Epidemiology and Pathophysiology

Congenital longitudinal lower extremity deficiencies are a group of disorders that are rarely encountered. The most common limb deficiency is fibular hemimelia, otherwise known as fibular hypoplasia or fibular deficiency, which occurs in 7.4 to 20 per one million live births [3]. The severity of disease occurs over a wide spectrum, from mild hypoplasia of the fibula to severe with complete absence of the entire bone. Congenital femoral deficiency and fibular hemimelia are found to be present in the ipsilateral limb in about 68% of cases. The overall incidence of femoral deficiencies is 1 in 50,000 and fibular hemimelia between 7.4 and 20 per million live births [4]. Similar to fibular hemimelia, femoral deficiencies also have a wide range of presentation, from mild hypoplasia causing congenital shortening of the long bone to severe dysplasia of the proximal femoral segment and the acetabulum, as with proximal focal femoral deficiency. Depending on the severity of these processes, other associated conditions can be present which include knee instability, absence of tibial spine, absence of anterior cruciate ligament, anterior and valgus bowing of the tibia, valgus deformity of the ankle, "ball and socket" ankle joint, subtalar/tarsal coalition, and absence of the lateral foot rays (metatarsals and phalanges) [1, 5, 6].

The cause of fibular hemimelia remains unknown. Most of the deformities occurs sporadically; however, chromosomal abnormalities, autosomal dominant, autosomal recessive, and X-linked transmission have been reported [7]. Other theories have been investigated, including vascular or mechanical interference of limb bud formation at the embryonic apical ectodermal ridge. Vascular abnormalities have been identified in patients with fibular hemimelia, showing a persistence of the embryonic vascular pattern with subsequent failure of development of a normal plantar arch, absence of the anterior tibial artery, and variations in the trifurcation of the popliteal artery [8]. The developmental fields defect theory hypothesizes that the fibula "controls" the development of the lateral foot raise, the anterior cruciate ligament, patella, proximal femur, acetabulum, and pubic bone while the tibia "controls" the development of the hallux and distal femur. This theory explains the associated deficiencies that are seen with fibular hemimelia. The etiology of congenital short femur is primarily sporadic, though rare cases of autosomal dominant transmission have been reported (see Fig. 9.1).

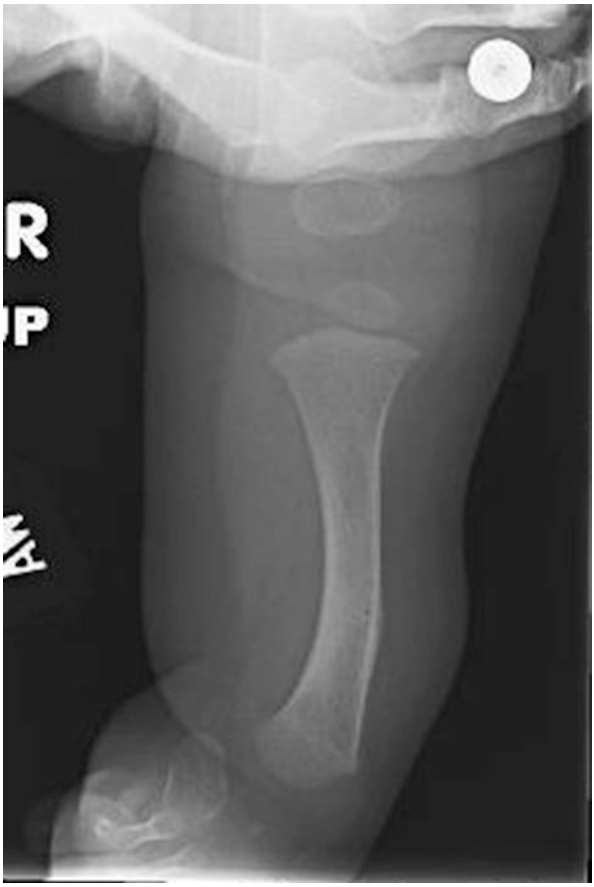


Fig. 9.1 Radiograph of calf with absence of fibula, knee to ankle. Image courtesy of Rebecca L. Carl, MD

Clinical Presentation: History and Physical

The clinical manifestations of lower limb deficiency are usually evident at birth. The presentation can be mild, with subtle differences in limb length, to more severe limb inequalities as with concomitant short or absent femur and fibula with associated anomalies of the hip, knee, ankle, and foot rays. Prenatal diagnosis with ultrasound has been utilized, though not always reliable [7]. A thorough maternal history as well as family history should be obtained. Involvement of multiple limbs is often related to autosomal dominant inheritance or influence of a teratologic agent.

Physical examination of the child will reveal a wide spectrum of deformity, depending upon the severity of the disease. Fibular hemimelia can present as hypoplasia, with subtle limb length inequality on examination or a mild anterior or anteromedial tibial bowing [6]. With dysplasia, abnormalities at the knee and ankle become more apparent. Knee abnormalities include absence of the anterior cruciate ligament and the posterior cruciate ligament, leading to knee instability. There may be variations in alignment, including genu valgum. Valgus deformity of the ankle may be associated with a fixed deformity or instability. Ankle abnormalities include a hemispherical articulation of the tibiotalar joint (ball and socket ankle) or valgus deformity which can also lead to instability or fixed deformity at the ankle joint (Fig. 9.2). As fibular hemimelia is a post-axial deformity, absence of lateral foot

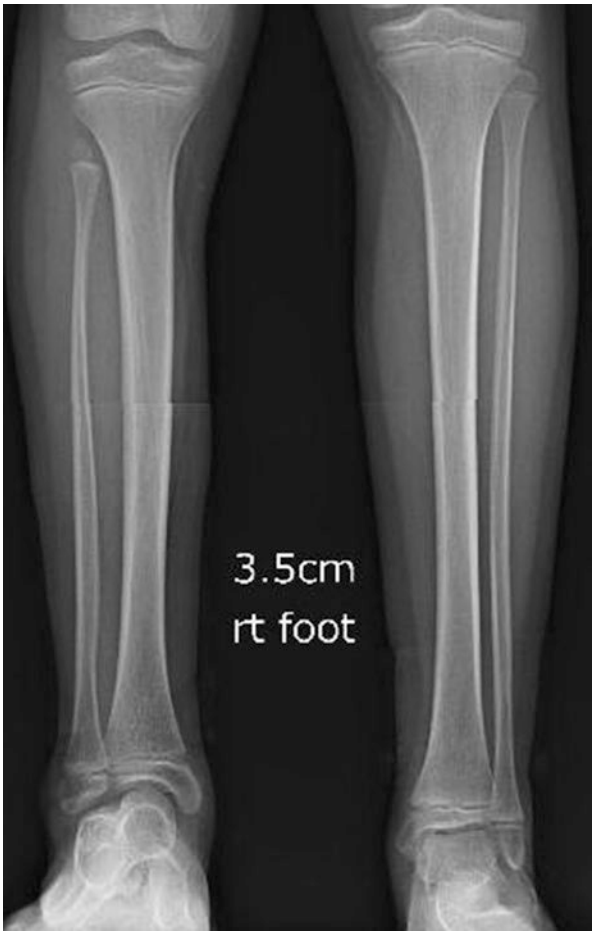


Fig. 9.2 Ball and socket ankle on the right

rays may be present. Equinovarus deformity of the foot (clubfoot) and tarsal coalition are other associated foot conditions. It is not uncommon to see bilateral involvement, with a prevalence reported from 9 to 52% [3, 9–11].

Fibular hemimelia often presents with ipsilateral abnormalities of the femur in up to 85% of cases [2]. As with fibular hemimelia, congenital short femur or proximal focal femoral deficiency also presents with varying degrees of deformity from mild hypoplasia to increasing severity of dysplasia of the femoral segment. Shortening and bowing of the femur may be evident through the physical exam. Less obvious, dysplasia and instability of the knee and hip are often associated with femoral shortening or deformity [12]. Evaluation at the hip is particularly important as with increasing severity, acetabular dysplasia and hip instability can limit the child's ambulation.

Upper extremity anomalies have been reported, including syndactyly, ulnar hemimelia, or amelia. Patients with bilateral congenital fibular deficiency have a higher incidence of upper extremity deficiencies [2, 13].

Evaluation

In addition to a thorough physical examination, plain radiographs of the involved limb permit the diagnosis and assessment of the congenital deficiency. As fibular hemimelia is not an isolated entity, radiographs of the full limb from hip to ankle and, separately, the foot are essential to complete evaluation (Fig. 9.3). Once standing, upright full length lower extremity radiographs, with the block beneath the foot to level the pelvis, are helpful to assess development of hip, knee, and ankle, as well as deviations from the normal mechanical alignment of the lower limb. These films can also help assess and quantify the limb length discrepancy. Alternatively, a CT scanogram or leg length radiographs with a radiopaque ruler may help quantify and track more exactly limb length discrepancy.

Magnetic resonance imaging (MRI) of the knee may be a useful modality to help assess the abnormalities that could be contributing to instability. Special attention is paid to presence or absence of the ACL, PCL, menisci, and hypoplasia or aplasia of the distal femoral condyles and surrounding muscles.

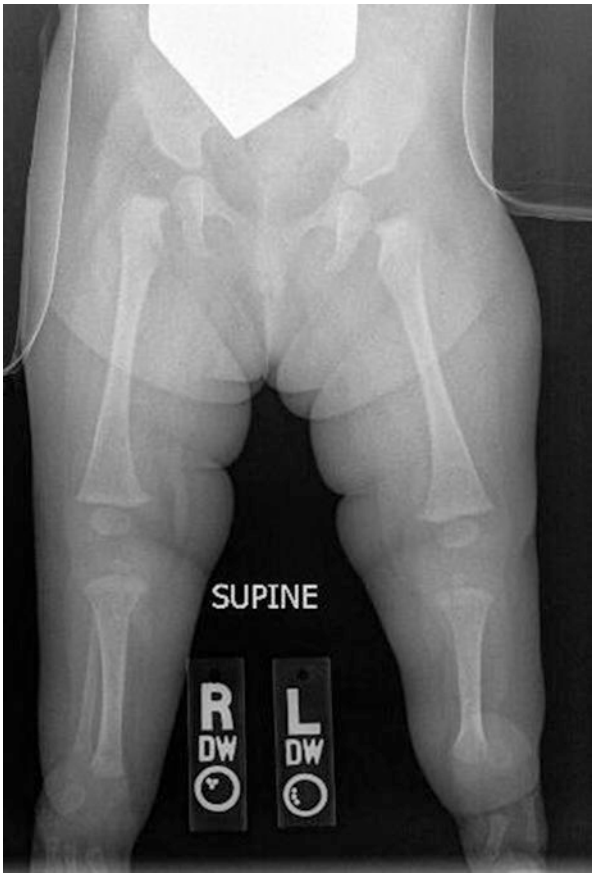


Fig. 9.3 Full length lower extremity films with absence of the left fibula on the left

Management

The goals of treatment in a child with a lower limb deficiency are to create or restore a weight-bearing lower extremity that allows for efficient ambulation or accommodation of a prosthesis that allows for functional gait. The management varies, depending on the severity of clinical presentation, the options available, and the shared decisions/choices of the family, the patient, and the medical team. The primary problems that need to be addressed are limb and joint alignment, limb length inequality, hip, knee and ankle instability, and contracture/mobility.

The principle of options to address limb length inequality helps guide treatment. The magnitude of femoral shortening and deformity in conjunction with the severity of fibular hypoplasia, the stability, mobility, and alignment of the joints guide both the goals and the options for intervention. If the abnormalities are mild and the patient has a stable knee and ankle and functional foot, shoe lifts or orthoses can help equalize leg length discrepancy. While usually not necessary, bracing can

address joint instability. Surgical reconstruction of joints and lengthening (or shortening either acutely of with growth by epiphysiodesis) are options which may be discussed with the family by specialist.

Clinical Pearls

- In the presence of clinically evident limb deformity or deficiency, radiographs of the entire limb and often the contralateral limb are helpful in discerning the underlying anomalies.
- The presence of a deficiency or complete absence of the fibula and/or femur is often associated with further limb abnormalities (joint, etc.) not always evident initially.
- Joint deficiencies or instability may be less evident on initial assessment but should be carefully reviewed by clinical and radiographic examination.
- Limb length inequality may vary with growth but most often remains proportional.
- Children are remarkably resilient and will readily compensate for deficiencies to obtain and maintain function.

References

1. Achterman C, Kalamchi A. Congenital deficiency of the fibula. J Bone Joint Surg. 1979;61B(2):133–7.
2. Birch JG, Lincoln TL, Mack PW, Birch CM. Congenital fibular deficiency. J Bone Joint Surg. 2011;93(12):1144–51. https://doi.org/10.2106/JBJS.J.00683.
3. Crawford DA, Tompkins BJ, Baird GO, Caskey PM. The long-term function of the knee in patients with fibular hemimelia and anterior cruciate ligament deficiency. J Bone Joint Surg Br. 2011;94B:328–33. https://doi.org/10.1302/0301-620X.94B3.
4. Shabtai L, Specht SC, Standard SC, Herzenberg JE. Internal lengthening device for congenital femoral deficiency and fibular hemimelia. Clin Orthop Relat Res. 2014;472(12):3860–8. https://doi.org/10.1007/s11999-014-3572-3.
5. Caskey PM, Lester EL. Association of fibular hemimelia and clubfoot. J Pediatr Orthop. 2002;2002(22):522–5. https://doi.org/10.1097/01.BPO.0000018991.02445.67.
6. Westberry DE, Carpenter AM, Barrera J, Westberry A. Management of tibial bow in fibular deficiency. J Pediatr Orthop. 2020 Apr;40(4):203–9. https://doi.org/10.1097/BPO.0000000000001182.
7. Fixsen JA. Major lower limb congenital shortening: a mini review. J Pediatr Orthop Br. 2003;12(1):1–12. https://doi.org/10.1097/01.bpb.0000043730.21564.92.
8. Levinsohn EM, Randall PA, Packard DS. Vascular dysgenesis associated with skeletal dysplasia of the lower limb. J Bone Joint Surg. 1980;62A(7):1123–9.
9. El-Sayed MM, Correll J, Pohlig K. Limb sparing reconstructive surgery and Ilizarov lengthening in fibular hemimelia of Achterman–Kalamchi type II patients. J Pediatr Orthop B. 2010;19(1):55–60. https://doi.org/10.1097/BPB.0b013e32832f5ace.

10. McCarthy JJ, Glancy GL, Chang F, Eilert R. Fibular hemimelia: comparison of outcome measurements after amputation and lengthening. J Bone Joint Surg. 2000;82A(12):1732–5.
11. Naudie D, Hamdy RC, Fassier F, Morin B, Duhaime M. Management of fibular hemimelia. J Bone Joint Surg Br. 1997;79:58–65.
12. Bowen JR, Kumar SJ, Orellana CA, Adreacchio A, Cardona JI. Factors leading to hip subluxation and dislocation in femoral lengthening of unilateral congenital short femur. J Pediatr Orthop. 2002;21:354–9.
13. Paley D. Surgical reconstruction for fibular hemimelia. J Children's Orthop. 2016;10(6):557–83. https://doi.org/10.1007/s11832-016-0790-0.

Chapter 10
Developmental Dysplasia of the Hip (DDH)

David K. Lyons, Meghan K. Urban, and Joseph A. Janicki

Brief Overview

Developmental dysplasia of the hip (DDH) refers to a spectrum of hip disorders with varying degrees of dysplasia of the femoral head or acetabulum. Presentation can vary from full dislocation in a newborn to mild acetabular changes in an adolescent or adult. Several terms are used to describe the hip throughout this spectrum of disease including subluxation, dysplasia, dislocation, or teratologic dislocation. Hip subluxation refers to a hip joint with slight displacement, but some maintained contact between articular surfaces. Hip dysplasia refers to a shallow or underdeveloped acetabulum. A dislocated hip refers to complete displacement of the femoral head, with no contact with the acetabulum. A teratologic dislocation is a more severe dislocation, with increased stiffness and inability to reduce the femoral head to its anatomic position within the acetabulum. Teratologic dislocations are typically dislocated in utero and associated with genetic and neuromuscular conditions.

DDH is one of the most common musculoskeletal disorder among newborns [1]. The initial hip instability is felt to be multifactorial in cause. This instability leads to alteration in normal hip positioning, which in turn affects the normal development and relationship of the femoral head and acetabulum. DDH is one of several "packaging deformities," which include congenital muscular torticollis, metatarsus adductus, and congenital knee dislocation. Frank instability and dislocation can be

D. K. Lyons
Department of Pediatric Orthopaedics, Ann and Robert Lurie Children's Hospital of Chicago, Chicago, IL, USA

M. K. Urban (✉)
Department of Physical Medicine and Rehabilitation, McGaw Medical Center of Northwestern Hospital, Chicago, IL, USA

J. A. Janicki
Ann and Robert Lurie Children's Hospital of Chicago, Chicago, IL, USA
e-mail: jjanicki@luriechildrens.org

J. F. Sarwark, R. L. Carl (eds.), *Orthopaedics for the Newborn and Young Child*,
https://doi.org/10.1007/978-3-031-11136-5_10

picked up on examination as an infant; however, subtle forms of dysplasia may be missed due to less obvious clinical presentation [2]. Early detection is crucial since the success of treatment is related to the severity of the condition and the child's age at presentation. The goal of treatment is to restore the "normal" position of the hip at the earliest age possible in order to ensure proper development of the femoral head and acetabulum.

Epidemiology

DDH is one of the most common orthopedic disorders found in newborns [1]. The estimated incidence of instability is 1 in 1000 newborns. This does not take into account the more subtle and clinically unnoticeable presentations, which puts the estimation of actual dysplasia as high as 1:50 or 1:100 depending on the inclusion criteria [2]. This pathology is most commonly seen in Native American and Laplanders and is uncommon in African Americans [3, 4]. One potential contributing factor is thought to be the cultural tradition of swaddling infants with their legs held together [5, 6]. Females also see a higher rate of hip dysplasia possibly due to the effects of maternal hormones at birth with rates as high as 6:1 compared with men [7]. The left hip is the most commonly affected, up to 60% of the time, with right side affected 20% and bilateral presentation in 20% of cases [8, 9]. It is felt that the left hip is affected more as the most common intrauterine position is left occiput anterior. In this position, the left hip is adducted against the lumbosacral spine of the mother [9].

The most notable risk factors for DDH include female gender, firstborn child, breech presentation, positive family history, and oligohydramnios. Firstborn children are thought to be at risk due to an unstretched uterus and other structures within the abdomen compressing the uterus. A similar mechanism is observed in oligohydramnios, in which decreased intrauterine fluid results in less space for the child, putting the hip at risk for abnormal positioning [9, 10]. Breech presentation puts the hip at risk for dysplasia regardless of vaginal or cesarean delivery [9]. The risk is higher with frank or single breech position when compared to footling breech position [11]. It is important to screen newborns for the above risk factors. The presence of one or more should raise suspicion and result in careful evaluation of the newborn hip. Clinical guidelines released by the American Academy of Orthopedic Surgeons (AAOS) support performing an ultrasound (2–6 weeks of age) or an X-ray (by 4 months of age) in infants with one or more of the following risk factors: breech presentation, family history, or history of clinical instability [12]. This recommendation was also endorsed by the American Academy of Pediatrics (AAP) and the Pediatric Orthopedic Society of North America (POSNA) [12].

Pathophysiology

Normal Anatomy

A normal hip consists of a spherical femoral head concentrically reduced within the hemispheric acetabulum. Maintenance of this relationship is important in the development of both the femoral head and acetabulum. The development of the hip joint occurs around the seventh week of gestation. The mesenchymal cells of this structure develop into a cartilaginous femoral head and acetabulum around the 11th week [13, 14]. Contact between the femoral head and acetabulum results in the concave hemispherical acetabular shape.

At birth, the acetabulum is composed of hyaline cartilage and is surrounded by a rim of fibrocartilage called the labrum. Growth of the acetabulum takes place at multiple growth centers. The shape of the acetabulum is typically determined by age 8, and the growth centers fully fuse during adolescence. The femoral head is also cartilaginous at birth, and an ossification center develops around 4–6 months after birth. Growth centers in the femoral head and greater and lesser trochanters all contribute to the growth and shape of the proximal femur (Fig. 10.1).

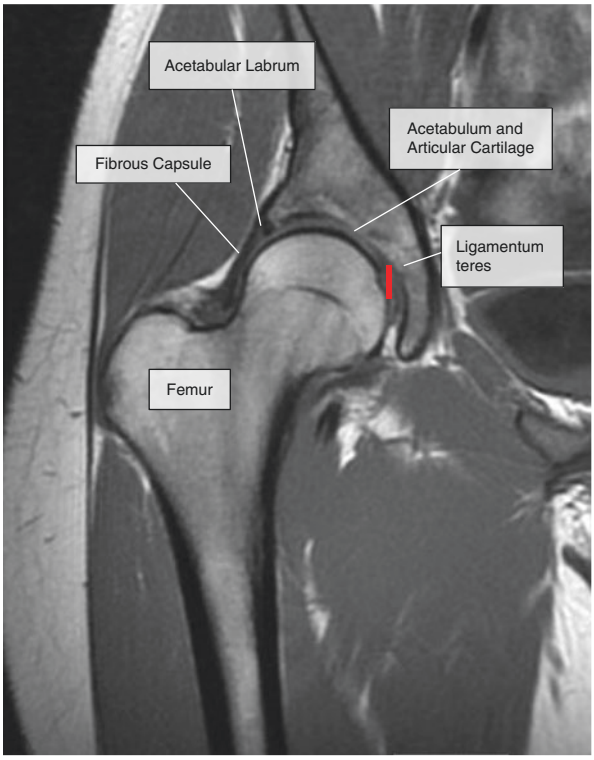


Fig. 10.1 Coronal T1 MRI of the right hip demonstrating the anatomy of a normal hip joint

Pathologic Changes

In DDH, multiple factors such as maternal or fetal laxity, intrauterine malpositioning, and postnatal positioning are thought to lead to instability and alter the normal femoral head and acetabular relationship. The alteration in normal positioning can lead to anatomic changes in the proximal femur such as increased anteversion or flattening of the head. Changes in the acetabulum can include increased acetabular anteversion, decreased concavity, or increased obliquity. The abnormal position can also result in hypertrophy of the ligamentum teres or transverse acetabular ligament, capsular laxity, and constriction of the capsule by the iliopsoas tendon. A ridge of thickened articular cartilage, called the limbus, can be formed by abnormal contact pressure. The dysplastic acetabulum may also be filled with a fibrofatty tissue called the pulvinar. All of the above can serve as blocks to concentric reduction, further potentiating the dysplasia (Fig. 10.2).

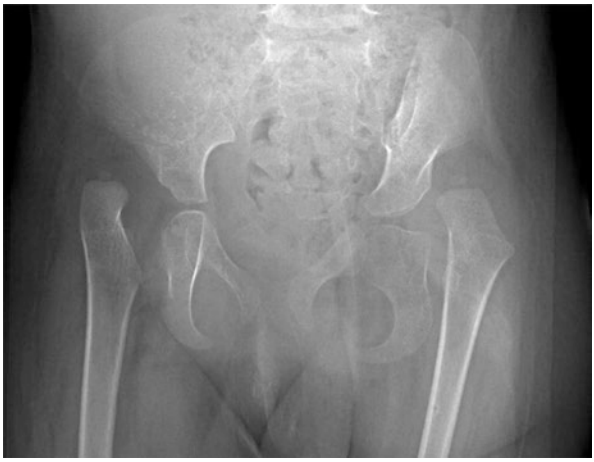


Fig. 10.2 X-ray AP pelvis of a 23-month-old with bilateral hip dislocations that are irreducible as a result of intraarticular obstacles. Obstacles to reduction can include an elongated ligamentum teres, inverted limbus, transverse acetabular ligament pulled upward, and fibrofatty pulvinar in the acetabulum

Clinical Presentation

History and Physical

Physical examination is paramount in the newborn and young infant as diagnosis is possible with several different tests. The two most common tests to aid in diagnosis are the Barlow and Ortolani tests [15, 16]. These two tests help identify the different phases of hip dysplasia which include a subluxatable, dislocatable, or dislocated hip. The Barlow test is performed with the child supine on the exam table. With the hips and knees flexed at 90°, the hip is slightly adducted and a steady posterior pressure is directed through the femur (Fig. 10.3). A clunk may be felt and is thought to be a "click of exit" when the femoral head subluxates or dislocates. A dislocatable hip is said to be "Barlow positive." The Ortolani test is also performed supine with the hips and knees flexed to 90°; however, the femur starts in a full abducted position. Elevation or anterior pressure is placed through the femur in an attempt to

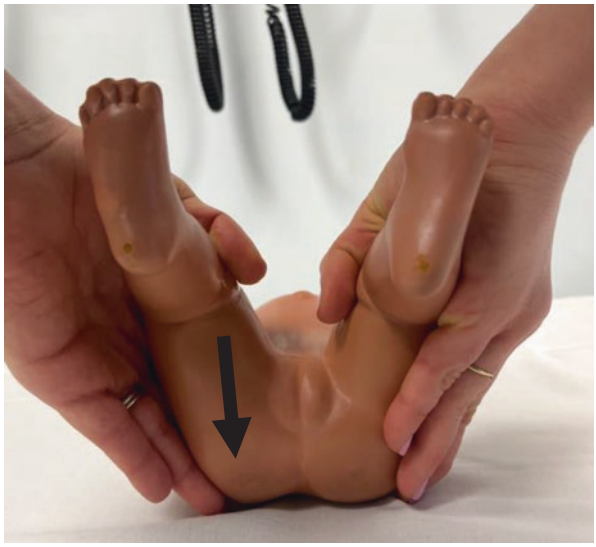


Fig. 10.3 The Barlow test. A positive Barlow test occurs when a palpable dislocation of the femur occurs

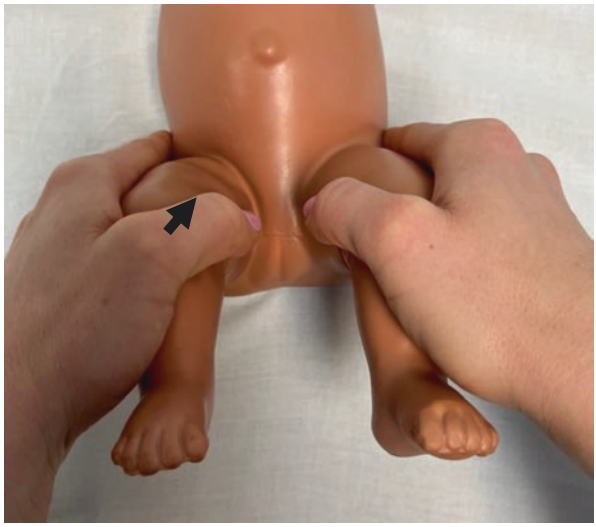


Fig. 10.4 The Ortolani test. A positive Ortolani test occurs when a palpable clunk is heard indicating the reduction of a dislocated hip into the acetabulum

reduce an already dislocated hip (Fig. 10.4). A "clunk of entry" may be felt as the femoral head is reduced in the acetabulum. When this reduction is possible, the hip is "Ortolani positive" and if a reduction is not felt it is "Ortolani negative." In summary, a hip that is reduced at rest but is able to be dislocated is Barlow positive (Ortolani negative) while the hip which is dislocated at rest but is able to be reduced is Ortolani positive (Barlow negative). Hip clicks felt throughout range of motion in examining the hips are nonspecific [17]. These tests are reliable up to 3 months of age. After this period, the pathologic changes to the hip make positive exam findings difficult.

Another common exam finding is the Galeazzi sign, which evaluates for limb length discrepancy. The child is placed supine on the exam table, hips are flexed to 90°, and the feet remain on the table. When examining the legs from the end of the table, one knee may appear "taller" than the other side and, in the case of DDH, may signify a dislocated hip (Fig. 10.5). Leg lengths may be measured as well, with a shorter side potentially due to a dislocated hip.

The Klisic test is an additional exam to help evaluate for DDH. In this exam, the examiner's long finger is placed at the tip of the greater trochanter, and the index finger is placed on the anterior superior iliac spine (ASIS). A line drawn between these points should point toward or proximal to the umbilicus; however, in a dislocated hip, this line will point between the umbilicus and the pubis (Fig. 10.6). This test may be helpful in detecting bilateral dislocations.

It is important to examine range of motion of both hips. Abduction to 70° is normal in a newborn. A significant limitation in abduction compared with the contralateral side may help identify a dislocated or subluxed hip. This is thought to be one of the most sensitive exam findings in an older infant but may be less sensitive in the first 6 weeks of life. This finding may be more subtle and difficult to detect in

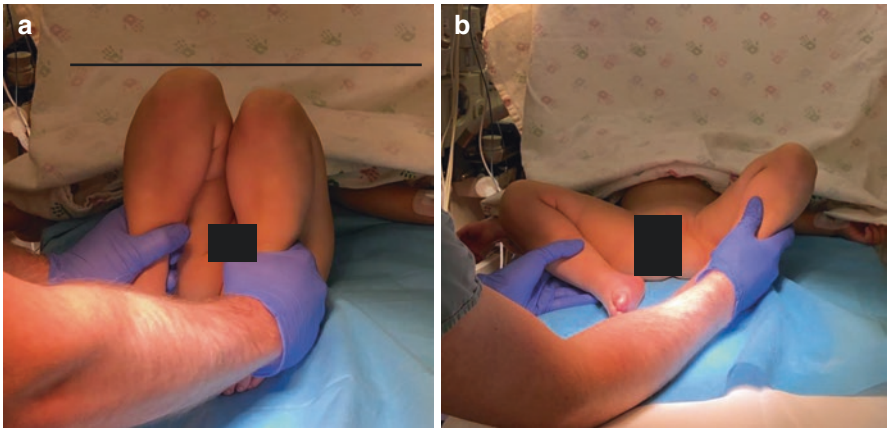


Fig. 10.5 A pre-operative examination of a patient with a left hip dislocation. Image (**a**) demonstrated a positive Galeazzi sign with apparent shortening of the femur as knees are flexed and pressed to buttocks. Image (**b**) demonstrated limited left hip abduction due to dislocation

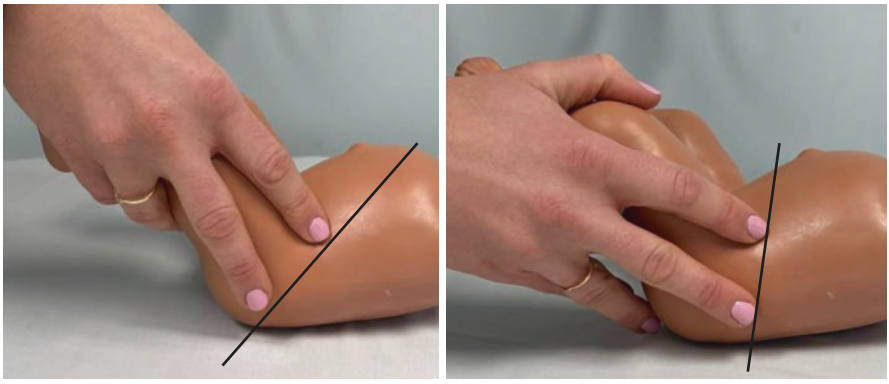


Fig. 10.6 The Klisic test. Developmental dysplasia of the hip is suspected when the imaginary line connecting the anterior superior iliac spine and greater trochanter passes below the umbilicus

bilateral dislocations. Asymmetry in the child's gluteal folds has also been described but is less reliable and specific than other findings.

As the child gets older and begins to ambulate, other exam findings may become more evident. Increases in pelvic obliquity or lumbar lordosis may be noted in response to hip contractures. A limb length discrepancy may again be noted, resulting in an ambulatory child unilaterally toe walking in an effort to compensate for the shortened extremity. Trendelenburg gait may be observed on the affected side due to abductor insufficiency.

Imaging

Several imaging studies are available to help diagnose DDH in the early phases, and other advanced imaging studies are available to help guide treatment. Ultrasound of the hip and pelvic X-rays are the most common modalities used in early diagnosis.

Ultrasound of the hip should be considered from birth to 4–6 months of age in children with a positive physical exam or significant risk factors as discussed above [12]. Radiographs are typically not useful in the prior to 6 months of age as the femoral head has not yet ossified and is not identifiable on X-ray. Since the ultrasound is a dynamic test, it can be used to see the hip moving in and out of the acetabulum. Ultrasound is also useful in monitoring reduction of the hip during treatment in a Pavlik harness.

The femoral head, labrum, ligamentum teres, hip capsule, and acetabular anatomy are all visible with an ultrasound. The examiner can identify a frank dislocation versus mild acetabular dysplasia. When examining a hip using ultrasound in a coronal view, the femoral head is typically bisected by a line drawn through the ilium. Measurements including the "alpha" and "beta" angles help in defining the amount of dysplasia. The alpha angle is defined as an angle created by a line drawn along the ilium and a line drawn along the bony acetabulum. A normal angle is greater than 60° (Fig. 10.7). The beta angle is created by measuring the angle created between a line through the labrum and one through the ilium. A normal angle is less than 55° (Fig. 10.7). Some physicians feel that adding dynamic adduction contributes to the sensitivity of these measurements [18]. Evaluation with ultrasound and measurement of these angles can help monitor treatment including observation or use of a Pavlik harness.

A commonly used classification system devised by Graf helps guide the treatment based on ultrasound measurements [19]. The Graf classification is broken up into four classes. In class I, the alpha angle is greater than 60° and beta angle is less

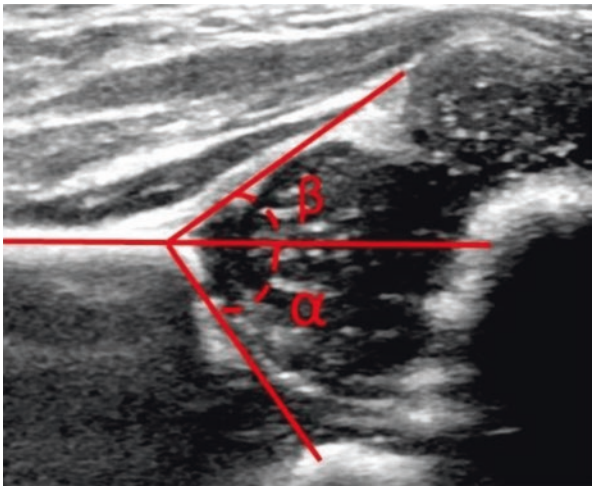


Fig. 10.7 Ultrasound demonstrating a coronal view of a normal hip joint. Alpha (α) angle should be greater than 60°. Beta (β) angle should be less than 55°

than 55°. This is felt to be a normal hip and no treatment is recommended. In class II, the alpha angle is between 43 and 60° and the beta angle is between 55 and 77°. This class has been further divided, but results in a significant gray area between observation and treatment with a Pavlik harness. Class III is a hip with an alpha angle less than 43° and a beta angle greater than 77°. This is felt to be a lateralized hip and is treated with a Pavlik harness. Class IV hips are dislocated, and the alpha and beta angles are unable to be measured. These are treated with Pavlik harness initially but failure to stabilize the hip may result in a closed or open reduction of the hip.

Universal screening of infants with an ultrasound of the hip has been previously considered in an effort to reduce the number of patients with DDH missed on clinical examination [2, 20]. This screening process has never implemented due to the limited evidence that it would prevent adverse outcomes. Both the AAOS and AAP have recommended against universal ultrasound screening in infants and base its use on risk factors (breech positioning and family history) or clinical hip instability [21]. The American Academy of Pediatrics recommends that ultrasound screening be considered between age 6 weeks and 6 months of age for infants with risk factors for hip dysplasia and a normal physical exam. Screening before 6 weeks is not recommended in this population given that mild abnormalities discovered on ultrasound will resolve in the first few months of life [22].

After ossification of the femoral head, typically at 4–6 months of age, radiographs become helpful in diagnosis. A simple AP view of the pelvis is sufficient for evaluation. Radiographs are recommended in a child with positive physical exam findings or previously identified DDH on ultrasound. An infant with obvious limb length discrepancy would also benefit from a pelvic radiograph to determine if DDH is the cause.

There are several radiographic clues to help evaluate for the presence of DDH. The ossification center of the femoral head should be present at 4–6 months of age; however, this may be delayed in the affected hip. Three different radiographic lines are typically described and used to evaluate the hip. These include Hilgenreiner's, Perkin's, and Shenton's lines. Hilgenreiner's line is created by drawing a horizontal line through bilateral triradiate cartilages (Fig. 10.8). Perkin's line is created by drawing a line perpendicular through the most lateral margin of the acetabulum (Fig. 10.8). In a normal hip, the ossification center of the femoral head should be inferior to Hilgenreiner's line and medial to Perkin's line. Shenton's line is created by following the line of the inferior border of the femoral neck and the superior margin of the obturator foramen. Shenton's line should be a continuous, smooth line. A disruption in this line signifies abnormal position of the hip (Fig. 10.8).

Other radiographic measurements including the acetabular index (AI) and center edge angle (CEA) of Wiberg are commonly described. The acetabular index is the angle created by the intersection of Hilgenreiner's line and a line drawn from the triradiate cartilage to the lateral border of the acetabulum. In patients older than 6 months, a normal angle is less than 25° [23] (Fig. 10.8). The center edge angle of Wiberg is the angle created by the intersection of Perkin's line and a line drawn

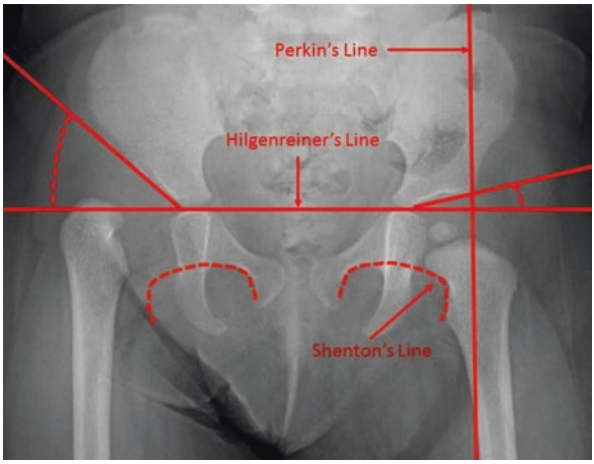


Fig. 10.8 Radiograph of a 15-month-old child demonstrating a right dislocated right hip with acetabular dysplasia. Note the delayed ossification of the femoral head, increased acetabular index, and disruption of Shenton's Line

from the center of the femoral head to the lateral edge of the acetabulum. This angle is greater than 20° in the normal hip [24].

Other imaging modalities useful in the treatment of DDH include arthrogram, CT scan, and MRI. These are typically performed by a pediatric orthopedic surgeon during treatment and are beyond the scope of this chapter.

Management

Treatment of developmental dysplasia of the hip is variable based on where the hip falls in the spectrum of disease and can range from nonoperative treatment, such as observation or the use of a Pavlik harness, to more invasive surgical treatment including pelvic or femoral osteotomies.

One of the most successful conservative treatments for DDH is the Pavlik harness, developed by Arnold Pavlik in 1946 [25]. The Pavlik harness is useful in infants, indicated in children younger than 6 months of age with a reducible hip (Fig. 10.9). The harness provides an early concentric reduction, which promotes normal acetabular development throughout the treatment course. Success rates from 65 to 100% have been reported, but results vary based on initial severity of dysplasia [26]. The Pavlik harness utilizes anterior and posterior straps which control hip flexion and abduction, respectively. The ideal position in the harness is hip flexion of 90–100° and hip abduction of 50°.

There is no consensus as to the daily amount of time in harness, as well as the duration of treatment. Typically, the harness is worn at least 23 h per day and 7 days per week. The reduction can be confirmed with ultrasound immediately following placement of the harness or at the first week follow-up visit. If the hip is found to be stable on the follow-up ultrasound, follow-up ultrasounds are performed every 2–3 weeks. If the hip remains dislocated or significantly subluxated at the initial

Fig. 10.9 Image demonstrating a child in a Pavlik harness

ultrasound in harness, follow-up ultrasounds occur more frequently and the duration of treatment may be altered, or the harness discontinued altogether if there is no improvement. The initial treatment duration is typically 6 weeks. If the initial treatment is successful, some surgeons recommend another 6 weeks in the harness and some recommend weaning from the harness over 2–6 weeks. Complications from this treatment include avascular necrosis (AVN) of the hip, transient femoral nerve palsy, and damage to the posterior acetabulum (Pavlik disease). AVN can be caused with the hips positioned in extreme or forced abduction, usually over 60°. This can result from over-tightening of the posterior strap [27, 28]. Femoral nerve palsy can result from hyperflexion of the hip or when the anterior strap is over-tightened [29]. Femoral nerve function is evaluated by observing the infant kicking their legs in the harness. If they are unable to extend their knee, treatment should be suspended. It may be resumed when the palsy has resolved. Hips that are not concentrically reduced and left in the Pavlik harness too long can lead to Pavlik disease in which the posterosuperior acetabulum erodes due to prolonged contact by the abnormally positioned hip [30].

Several alternative bracing options exist to help treat DDH. Splints such as the Ilfeld, Von Rosen, Hoffman-Daimler, and other semi rigid abduction orthosis are available. One study showed 93% success rate using a semirigid hip abduction orthosis in hips that failed treatment using a Pavlik harness [31].

When conservative treatments do not achieve the desired result or fail altogether, there are several surgical options to help address this. These treatments are typically based on the age of the patient and where they fall in the spectrum of disease.

In hips that fail treatment in a Pavlik harness or patients who are 6–18 months of age, a closed reduction is a suitable treatment option. A hip that is reducible on

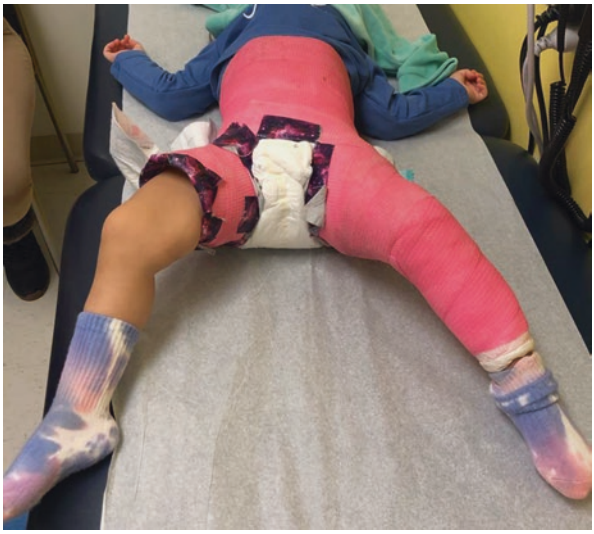


Fig. 10.10 Image demonstrating a child in a hip spica cast

physical exam is more likely to be treated successfully using this method. The hip is reduced under anesthesia and held in a reduced position using a hip spica cast (Fig. 10.10). An arthrogram, in which radiopaque dye is injected into the hip joint, can be useful in identifying an appropriate reduction or detecting pathologic structures blocking reduction. Once the reduction is performed and the cast placed, a CT or MRI of the hip is typically performed to confirm reduction. Children are typically kept in the initial cast for 6 weeks, then taken for a hip examination under anesthesia and spica cast change. The total duration of treatment is approximately 3 months.

In hips that are not amenable to closed reduction, or children who present later in life, an open reduction may be the next treatment option. In this surgery, the hip joint is opened, pathologic obstructions to reduction are removed, and the femoral head is gently guided back into the acetabulum. Surgeons may choose from different approaches, medial or anterior, based on surgeon preference or patient age. These children are also placed in a hip spica cast after surgery to hold the hip in a reduced position. Femoral shortening osteotomies may also need to be performed during this procedure to help decrease the contact pressures of the hip joint when reduced.

In older children (>18 months), there is less potential for acetabular remodeling from the above procedures. Older children with residual dysplasia, or younger children with severe dysplasia, may benefit from pelvic and/or femoral osteotomies to improve their anatomy. Several techniques are available to reshape, redirect, or reconstruct the acetabulum. The type of surgery and techniques are based on the patient's age, severity of dysplasia, and surgeon preference [26].

Hips should be continuously monitored after treatment to ensure appropriate development of the hip. Clinical and radiographic evaluations should continue until the child reaches skeletal maturity [32].

Natural History, Primary and Secondary

The goal of treatment is to improve stability of the hip joint by attempting to recreate normal hip anatomy. Abnormal anatomy of this hip joint may result in hip dysfunction and/or early osteoarthritis. Many studies have examined the relationship between acetabular dysplasia and osteoarthritis and found that dysplasia may lead to early arthritis of the hip. There is some evidence that radiographic findings, such as a center edge angle less than 20°, may predict osteoarthritis of the hip before age 65 [24, 33, 34]. By diagnosing and treating this problem early in life, we hope to decrease the risk of hip dysfunction and early onset arthritis of the hip.

References

1. Sankar WN, Weiss J, Skaggs DL. Orthopaedic conditions in the newborn. J Am Acad Orthop Surg. 2009;17(2):112–22.
2. Rosendahl K, Markestad T, Lie RT. Ultrasound screening for developmental dysplasia of the hip in the neonate: the effect on treatment rate and prevalence of late cases. Pediatrics. 1994;94(1):47–52.
3. Coleman SS. Congenital dysplasia of the hip in the Navajo infant. Clin Orthop Relat Res. 1968;56:179–93.
4. Skirving AP, Scadden WJ. The African neonatal hip and its immunity from congenital dislocation. J Bone Joint Surg Br. 1979;61-B(3):339–41.
5. Mahan ST, Kasser JR. Does swaddling influence developmental dysplasia of the hip? Pediatrics. 2008;121(1):177–8.
6. Wang E, Liu T, Li J, Edmonds EW, Zhao Q, Zhang L, et al. Does swaddling influence developmental dysplasia of the hip? An experimental study of the traditional straight-leg swaddling model in neonatal rats. J Bone Joint Surg Am. 2012;94(12):1071–7.
7. Carter CO, Wilkinson JA. Genetic and environmental factors in the etiology of congenital dislocation of the hip. Clin Orthop Relat Res. 1964;33:119–28.
8. Dunn PM. The anatomy and pathology of congenital dislocation of the hip. Clin Orthop Relat Res. 1976;119:23–7.
9. Dunn PM. Perinatal observations on the etiology of congenital dislocation of the hip. Clin Orthop Relat Res. 1976;119:11–22.
10. Manoukian D, Rehm A. Oligohydramnios: should it be considered a risk factor for developmental dysplasia of the hip? J Pediatr Orthop B. 2019;28(5):442–5.
11. Suzuki S, Yamamuro T. Correlation of fetal posture and congenital dislocation of the hip. Acta Orthop Scand. 1986;57(1):81–4.
12. Orthoguidelines.org. 2019. http://www.orthoguidelines.org/guideline-detail?id=1222.
13. Watanabe RS. Embryology of the human hip. Clin Orthop Relat Res. 1974;98:8–26.
14. Strayer LM Jr. Embryology of the human hip joint. Clin Orthop Relat Res. 1971;74:221–40.
15. Ortolani M. Congenital hip dysplasia in the light of early and very early diagnosis. Clin Orthop Relat Res. 1976;119:6–10.
16. Barlow TG. Congenital dislocation of the hip in the newborn. Proc R Soc Med. 1966;59(11):1103–6.
17. Bond CD, Hennrikus WL, DellaMaggiore ED. Prospective evaluation of newborn soft-tissue hip “clicks” with ultrasound. J Pediatr Orthop. 1997;17(2):199–201.

18. Clarke NM, Harcke HT, McHugh P, Lee MS, Borns PF, MacEwen GD. Real-time ultrasound in the diagnosis of congenital dislocation and dysplasia of the hip. J Bone Joint Surg Br. 1985;67(3):406–12.
19. Graf R. Classification of hip joint dysplasia by means of sonography. Arch Orthop Trauma Surg. 1984;102(4):248–55.
20. Holen KJ, Tegnander A, Bredland T, Johansen OJ, Saether OD, Eik-Nes SH, et al. Universal or selective screening of the neonatal hip using ultrasound? A prospective, randomised trial of 15,529 newborn infants. J Bone Joint Surg Br. 2002;84(6):886–90.
21. Orthoguidelines.org. 2019. http://www.orthoguidelines.org/guideline-detail?id=1221.
22. Shaw BA, Segal LS. Evaluation and referral for developmental dysplasia of the hip in infants. Pediatrics. 2016;138(6).
23. Tonnis D. Normal values of the hip joint for the evaluation of X-rays in children and adults. Clin Orthop Relat Res. 1976;119:39–47.
24. Wiberg G. Studies on dysplastic acetabula and congenital subluxation of the hip joint with special reference to the complication of osteoarthritis. Acta Chir Scand. 1939;83:7–135.
25. Pavlik A. Stirrups as an aid in the treatment of congenital dysplasias of the hip in children. By Arnold Pavlik, 1950. J Pediatr Orthop. 1989;9(2):157–9.
26. Casteneda P. Developmental dysplasia of the hip. In: Martus JE, editor. Orthopaedic knowledge update: pediatrics 5. Rosemont, IL: American Academy of Orthopaedic Surgeons; 2016. p. 245–57.
27. Kalamchi A, MacEwen GD. Avascular necrosis following treatment of congenital dislocation of the hip. J Bone Joint Surg Am. 1980;62(6):876–8.
28. Suzuki S, Yamamuro T. Avascular necrosis in patients treated with the Pavlik harness for congenital dislocation of the hip. J Bone Joint Surg Am. 1990;72(7):1048–55.
29. Murnaghan ML, Browne RH, Sucato DJ, Birch J. Femoral nerve palsy in Pavlik harness treatment for developmental dysplasia of the hip. J Bone Joint Surg Am. 2011;93(5):493–9.
30. Jones GT, Schoenecker PL, Dias LS. Developmental hip dysplasia potentiated by inappropriate use of the Pavlik harness. J Pediatr Orthop. 1992;12(6):722–6.
31. Swaroop VT, Mubarak SJ. Difficult-to-treat Ortolani-positive hip: improved success with new treatment protocol. J Pediatr Orthop. 2009;29(3):224–30.
32. Modaressi K, Erschbamer M, Exner GU. Dysplasia of the hip in adolescent patients successfully treated for developmental dysplasia of the hip. J Child Orthop. 2011;5(4):261–6.
33. Stulberg SD, Harris WH. Acetabular dysplasia and the development of osteoarthritis of the hip. In Proceedings of the second open scientific meeting of the Hip Society, St. Louis; 1974.
34. Cooperman D. How good is the evidence linking acetabular dysplasia to osteoarthritis? J Pediatr Orthop. 2019;39(6):S20–2.

Chapter 11
Upper Limb Deficiencies

Alicia C. Zolkoske

Introduction

Upper limb deficiencies are classified according to the International Organization for Standardization (ISO) [1]. These classifications delineate transverse or longitudinal deficiencies and the affected level involved. Transverse deficiencies of limbs are normally developed up to an amputation-like level, after which no further skeletal elements are seen. Longitudinal deficiencies involve absence or alteration of elements within the long axis of a limb.

Radial Deficiencies

Clinical Findings

Radial deficiencies may be clinically identified by shortening of the forearm, bowing of the ulna, or radial deviation of hand position. Affected limbs are sometimes referred to as radial club hands. The ulna in affected children is usually about two-thirds the length of a non-affected ulna, leading to the appearance of a shortened forearm [2]. There may also be elbow flexion contracture, missing digits of the hand, or dysplasia of digits such as hypoplasia or absence of the thumb. The estimated incidence of congenital radial deficiency is found to be 1 in 30,000 to 1 in 100,000 live births [3].

A. C. Zolkoske (✉)
Department of Orthopedic Surgery, Children's Hospital of Wisconsin/Medical College of Wisconsin, Milwaukee, WI, USA
e-mail: azolkoske@chw.org

J. F. Sarwark, R. L. Carl (eds.), *Orthopaedics for the Newborn and Young Child*,
https://doi.org/10.1007/978-3-031-11136-5_11

Table 11.1 Bayne classification of radial deficiencies

Type	Characteristic findings
0	Hypoplasia of the scaphoid; normal length of radius
I	Shortened radius at distal physis; may have thumb hypoplasia
II	Shortened radius at proximal and distal physes
III	Partial absence of radius; usually missing distal two-thirds with absence of distal physis
IV	Complete absence of radius

Table 11.2 Buck-Gramcko Thumb Grades [4]

Grade	Characteristic findings
I	I. Thumb slightly smaller or narrower than normal with otherwise normal joint and motion
II	II. Thumb is smaller than normal; hypoplastic thenar intrinsic muscles and often first web space contracture; unstable metacarpal phalangeal joint
III	III. Thumb is short and unstable; severe web space contracture with complete absence of thenar muscles
IV	IV. Referred to as "pouce flottant" or floating thumb; one to two hypoplastic phalanges without tendon or muscle connection
V	V. Complete absence/aplasia of thumb

Classification

Radial deficiencies may be further classified according to the Bayne Classification (Table 11.1). Along the spectrum of deficiencies, Type IV is the most severe and most common [3].

Further grading of radial deficiency based on thumb anatomy was proposed by Buck-Gramcko (Table 11.2).

Evaluation/Risk Factors

Patients with apparent radial deficiencies should undergo radiographic evaluation with AP and lateral X-rays of the entire arm and hand. Additional evaluation should include renal ultrasound, cardiac echocardiogram, and lab testing including a complete blood count due to risk of associated syndromes. Wahab et al. found that about 40% of patients with unilateral radial deficiency and 27% with bilateral radial deficiency have associated congenital anomalies involving cardiac, renal, anal, skeletal, and hematopoietic system [5]. Known associated syndromes include:

– Holt-Oram syndrome: radial deficiency along with cardiac septal defect/heart block.
– Fanconi anemia: radial deficiency along with pancytopenia. Patients with presumed Fanconi anemia should have a Fanconi screen and chromosomal breakage test in addition to typical testing.

– VACTERL syndrome: vertebral anomalies, anal atresia, cardiac abnormalities, tracheoesophageal fistula, renal agenesis, and limb defects.
– VATER syndrome: vertebral anomalies, anal atresia, tracheoesophageal fistula, esophageal atresia, renal agenesis.
– Thrombocytopenia-absent radius syndrome (TAR)—thrombocytopenia with total absence of radius.

TAR does not result in thumb hypoplasia but instead leads to a flat, broad thumb [6].

Thalidomide is a known teratogen with 60% of children having radial dysplasia if their mother took thalidomide [7]. Patients affected by thalidomide present with symmetrical pattern of deficiency or polydactyly on the preaxial side of both arms and legs [8]. Exposure to misoprostol may result in vascular disruption with asymmetric digit loss, constriction rings, and/or syndactyly [9]. Amniotic bands or congenital constriction bands can present with deficiency at any level of the upper limb. This may range from narrowing to complete amputation.

Treatment

Mild forms of radial deficiency may be conservatively managed with stretching, bracing, or orthotics/prosthetics. Treatment of more significant radial deficiency is performed with surgical centralization to reposition the hand at the distal end of ulna as well as stabilization of the articulation between the forearm and hand. Thumb reconstruction may be required to enhance function.

Ulnar Deficiency

Clinical Findings

Ulnar deficiency may be suspected clinically due to shortened forearm, ulnar digit deficiency, and/or radial bowing. There may be radial head dislocation or elbow contracture as well. In contrast to radial deficiency, hand position is usually relatively well aligned at the wrist. Incidence of ulnar deficiency is 1 in 100,000 live births [10].

Classification

In addition to radial deficiency classification, Bayne also characterized ulnar deficiency based on ulna and elbow structure (Table 11.3) [11]. Cole and Manske characterized ulnar deficiency based on thumb/first web deficiency (Table 11.4) [12].

Table 11.3 Bayne classification

Type	Characteristic findings
0	Deficiency of carpus
I	Shortened ulna
II	Shortening from distal ulna with absent distal epiphysis
III	Complete absence of ulna
IV	Radiohumeral synostosis

Table 11.4 Cole and Manske

Type	Characteristic findings
A	Normal thumb and first web space
B	Mild first web and thumb deficiency
C	Moderate to severe first web and thumb deficiency
D	Absent thumb

Evaluation/Risk Factors

Evaluation for ulnar deficiency should consist of AP and lateral radiographic evaluation of the entire arm and hand in question. Ulnar deficiency is not associated with systemic conditions to the same extent as radial deficiencies; therefore, additional testing will be determined based on abnormal clinical findings.

Ulnar deficiency may be seen in Cornelia de Lange syndrome, as well as numerous rare syndromes including mesomelic dwarfism, Pallister-Hall syndrome, and Schinzel-Giedion syndrome.

Longitudinal ulnar deficiency may be associated with a variety of other musculoskeletal abnormalities such as coexisting radial deficiency, fibular hypoplasia, partial longitudinal deficiency of femur, congenital coxa vara, phocomelia, or cleft palate [13].

Treatment

Treatment of ulnar deficiency may be conservative pending functional capacity. Severe cases may require surgical intervention such as rotational osteotomies or syndactyly release.

Humeral Deficiency

Humeral deficiency is less common than forearm deficiencies. Congenital absences are usually sporadic unless associated with radial deficiency [14]. A thorough physical exam is required to determine need for additional imaging or testing.

References

1. International Organization for Standardization. ISO 8548-1: Prosthetics and orthotics—Limb deficiencies, Part 1: Method of describing limb deficiencies present at birth. Geneva, Switzerland: International Organization for Standardization; 1989. p. 1–6.
2. Vilkki SK. Distraction and microvascular epiphysis transfer for radial club hand. J Hand Surg. 1998;3:445–52.
3. Bayne LG, Klug MS. Long-term review of the surgical treatment of radial deficiencies. J Hand Surg Am. 1987;12:169–79.
4. Buck-Gramcko D. Congenital absence and hypoplasia of the thumb. In: Strickland JW, editor. The thumb. Edinburgh, Scotland: Churchill Livingston; 1994. p. 45–65.
5. Wahab S, Ullah E, Khan RA, Sherwani MK. Radial club hand—a case report and review of literature. Bombay Hosp J. 2009;51:94–6.
6. Goldfarb CA, Wustrack R, Pratt JA, Mender A, Manske PR. Thumb function and appearance in thrombocytopenia: absent radius syndrome. J Hand Surg Am. 2007;32(2):157–61.
7. Lamb DW. Radial club hand: a continuing study of sixty-eight patients with one hundred and seventeen club hands. J Bone Joint Surg Am. 1977;59.
8. Kallen B, Rahmani TM-Z, Winberg J. Infants with congenital limb reduction registered in the Swedish Register of Congenital Malformations. Teratology. 1984;29:73–85.
9. Gonzalez CH, Marques-Dias MJ, Kim CAE, et al. Congenital abnormalities in Brazilian children associated with misoprostol misuse in the first trimester of pregnancy. Lancet. 1998;351:1624–7.
10. Birch-Jensen A. Congenital deformities of the upper extremities. Odense, Denmark: Andelsbogtrykkeriet; 1949. p. 411–24.
11. Bayne LG. Ulnar club hand (ulnar deficiencies). In: Green DP, editor. Operative hand surgery, vol. 11. New York, NY: Churchill Livingstone; 1982. p. 245–57.
12. Cole RJ, Manske PR. Classification of ulnar deficiency according to the thumb and first web. J Hand Surg [Am]. 1997;22:479–88.
13. Kuz J, Engels J. Longitudinal ulnar deficiency. In: Smith D, Michael J, Bowker J, editors. Atlas of amputations and limb deficiencies. 3rd ed. Rosemont, IL: American Academy of Orthopedic Surgeons; 2004. p. 869–73.
14. Goldberg MJ, editor. The dysmorphic child: an orthopedic perspective. New York, NY: Raven Press; 1987. p. 301, 324–57.

Chapter 12
Polydactyly and Syndactyly of the Hand

Erik C. B. King and Muhammad Y. Mutawakkil

Brief Overview of Condition

Hand anomalies are the second most common musculoskeletal congenital conditions encountered in the newborn, and polydactyly and syndactyly are the most common hand anomalies. Polydactyly is defined as a duplication of fingers in the hand, and syndactyly is defined as a fusion of the soft tissue and/or skeletal elements of adjacent digits. Polysyndactyly refers to syndactyly and polydactyly in the same hand. Both polydactyly and syndactyly can occur in isolation or as part of a syndrome. Because both congenital differences can potentially cause significant limitations in normal hand function, it is important to establish the diagnosis early and develop a treatment plan. Corrective surgery is usually recommended and should be timed so as to minimize functional limitations. Discussions about timing usually focus on ensuring that the child achieves developmental milestones, while also minimizing the risks of surgery and anesthesia.

E. C. B. King (✉)
Department of Orthopaedic Surgery, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA
e-mail: eking@luriechildrens.org

M. Y. Mutawakkil
Department of Orthopaedic Surgery, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA

Department of Orthopaedic Surgery, Northwestern University Feinberg School of Medicine, Chicago, IL, USA
e-mail: muhammad.mutawakkil@northwestern.edu

J. F. Sarwark, R. L. Carl (eds.), *Orthopaedics for the Newborn and Young Child*,
https://doi.org/10.1007/978-3-031-11136-5_12

Background Including Epidemiology and Pathophysiology

The incidence of polydactyly varies by ethnic groups. It is estimated to be 1 in 300 in African-descent populations and 1 in 3000 in Caucasian populations [1, 2]. In children of African descent, polydactyly is more common on the ulnar aspect of the hand, whereas in Caucasian children, polydactyly is more common on the radial aspect of the hand. Indeed, the presence of ulnar polydactyly in a Caucasian child should raise suspicion that the child has an underlying syndrome. Polydactyly can be an isolated congenial anomaly or a component of a syndrome. Through advances in the genetics and molecular biology, several genes that play a role in the development of polydactyly have been identified. The responsible genes include GLI3 gene, the ZNF141 gene, the MIPOL1 gene, and the PITX1 gene [3]. Syndromes associated with polydactyly include Apert syndrome, Carpenter syndrome, Pfeiffer syndrome, Smith Lemli Opitz syndrome, Pallister Hall syndrome, Poland syndrome, Bardet Biedl syndrome, Ellis–van Creveld syndrome, Laurence-Moon-Biedl syndrome, and trisomy 13 [1, 2, 4].

The incidence of syndactyly is reported to be 1 in 2000 live births [4]. Like polydactyly, the incidence of syndactyly varies by ethnic group. It is ten times more common in Caucasian individuals than in African-descent individuals [1]. Positive family history is reported in 10–40% of cases, and approximately 50% of syndactyly cases are bilateral. Although syndactyly exhibits an autosomal dominant pattern of inheritance, variable expressivity and incomplete penetrance is seen, resulting in variable phenotype within a family and a 2:1 preponderance in males. Syndactyly can be an isolated congenital anomaly or a component of a syndrome.

During the early stages of fetal development, hand and feet are initially webbed together extending to the fingertips resembling a mitten. The expression of apical ectodermal ridge (AER) maintenance factor causes the webbing to persist early in gestation. However, during normal embryologic development, the production of AER ceases in a programmed coordinated fashion. Cessation of AER production results in apoptosis (also known as programmed cell death) of the cells in the web. In turn, the tissue in the web recedes beginning distally and progressing proximally, and the web space is formed. Embryologic events that lead to the failure of normal apoptosis cause syndactyly.

Clinical Presentation: History and Physical

Polydactyly

Polydactyly is classified based on the radial to ulnar location of the duplicated digit. Radial polydactyly, also known as preaxial polydactyly, occurs along the radial side of the hand. Ulnar polydactyly, also known as postaxial polydactyly, involves the

ulnar side of the hand. Central polydactyly is less common and involves duplication of one of the three central digits. Central polydactyly is often coexistent with syndactyly.

Radial Polydactyly (Preaxial Polydactyly)

On clinical examination, radial polydactyly resembles a duplication of the thumb (Fig. 12.1). However, parents should be counseled that this is in fact not a duplication of a normal thumb, but rather abnormal development of two thumbs. Neither of the thumbs is normal, and even following reconstructive surgery, the residual thumb is always more narrow and stiffer than a normal thumb. Some hand specialists believe that "split thumb" is a more appropriate term for this anomaly.

Radial polydactyly may involve any level of the thumb and is commonly described by the Wassel classification [5] (Fig. 12.2). This classification scheme is based on the anatomic level of duplication and the number of supernumerary bones. Type IV is the most common type.

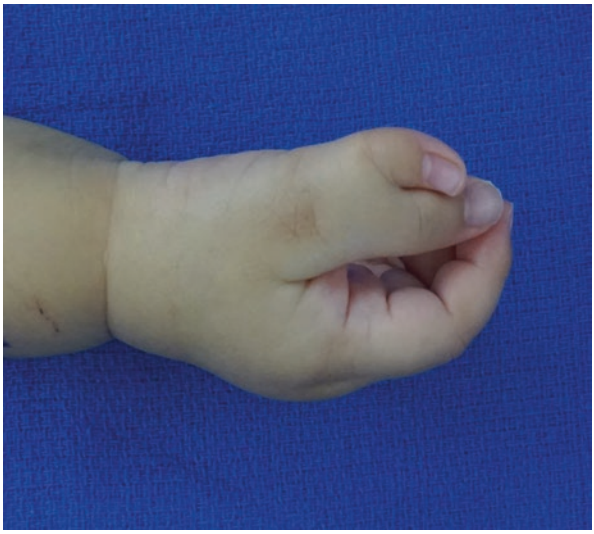


Fig. 12.1 Radial polydactyly, Wassel type IV

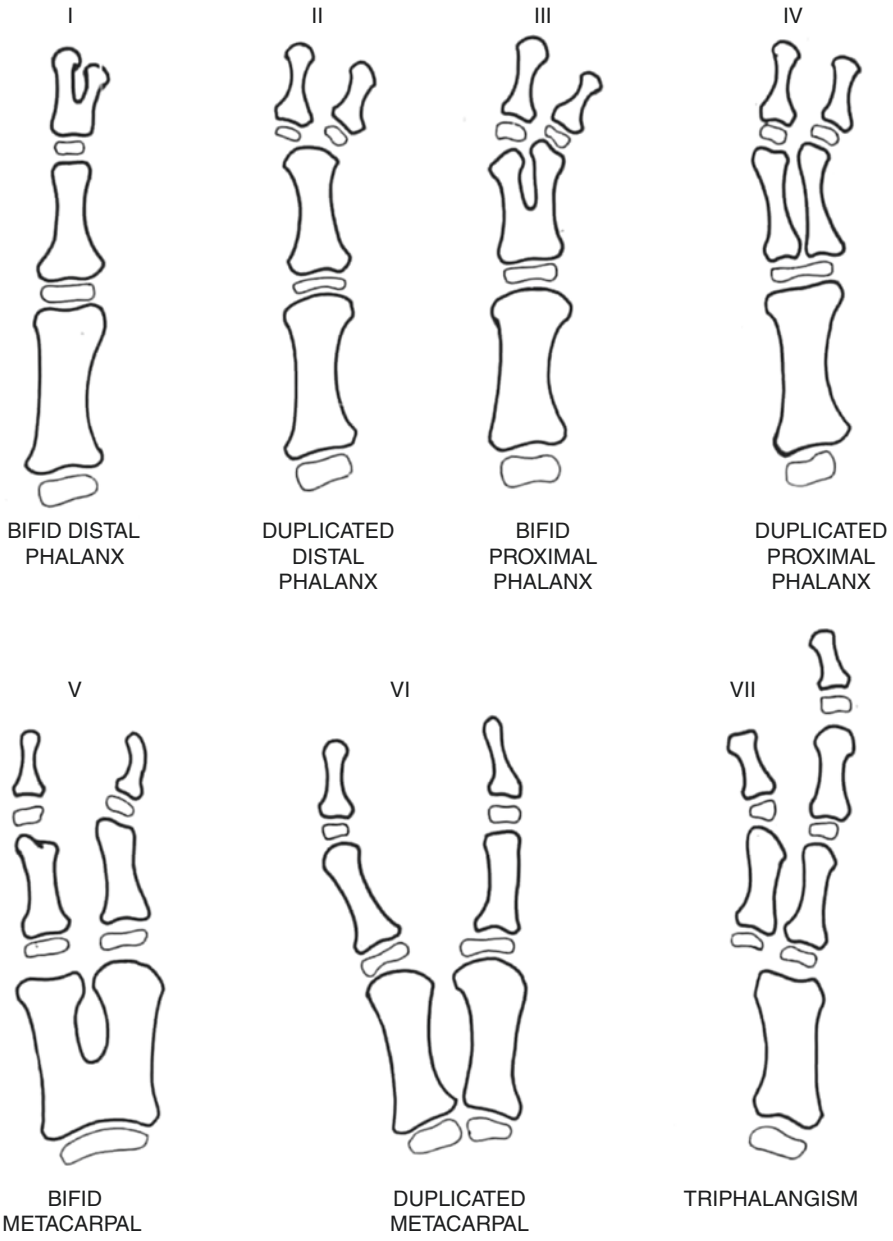


Fig. 12.2 Seven types of thumb polydactyly distinguished [5]. Reprinted with permission from Wassel HD. The results of surgery for polydactyly of the thumb: A review. Clinical Orthopaedics and Related Research, Vol. 64, pgs. 175–193, © 1969, with permission from Wolters Kluwer Health, Inc.

Central Polydactyly

Central polydactyly is an uncommon form of polydactyly that affects the index, ring, or long fingers (Fig. 12.3). Central polydactyly makes up approximately 5–15% of all polydactylies [6, 7]. Central polydactyly is classified into three types. Type I polydactylies are ones in which the supernumerary finger is not attached to the adjacent finger by osseous or ligamentous attachments. Type II polydactylies have normal-appearing osseous and soft tissue structures within the supernumerary digit and share a joint, a bifid metacarpal, or phalanx with the adjacent finger. Type II is further subdivided by the absence (type IIa) or presence (type IIb) of associated syndactyly. Type III polydactylies consist of completely duplicated rays, including fully formed metacarpals.

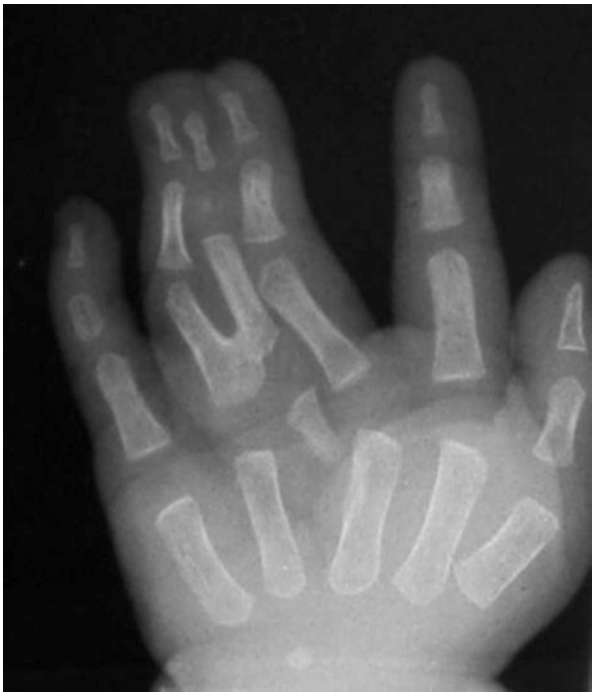


Fig. 12.3 Central polydactyly between middle and long fingers. There is also syndactyly involving all three fingers

Ulnar Polydactyly (Postaxial Polydactyly)

Ulnar polydactyly is the most common form of polydactyly. This anomaly presents as a supernumerary digit on the ulnar border of the affected hand. Ulnar polydactylies are classified as Type A, which is a fully developed finger, or Type B, which comprises a rudimentary nubbin or pedunculated finger attached to the lateral aspect of the finger via a small soft tissue stalk (Fig. 12.4).

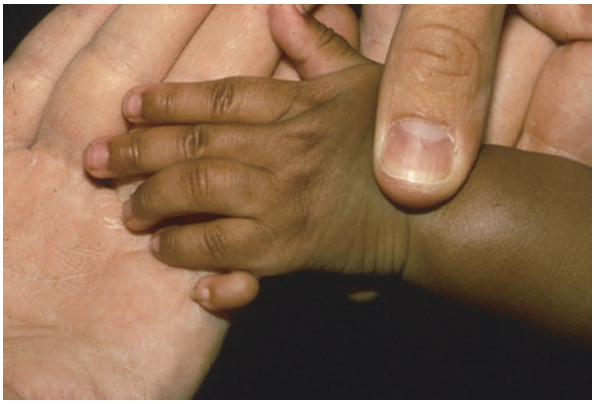


Fig. 12.4 Ulnar polydactyly, type B. The rudimentary polydactyly digit (nubbin) is connected by a narrow soft tissue stalk with no articulation to the hand

Mirror Hand

Mirror hand is an extremely rare form of polydactyly in which there is symmetric duplication of the hand around the mid-axis of the hand. The central finger is often bordered by three symmetric fingers on each side (Fig. 12.5). Despite the seven digits, there is no functional thumb. Mirror hand is also associated with duplication of the ulna bone in the forearm without a true radius.

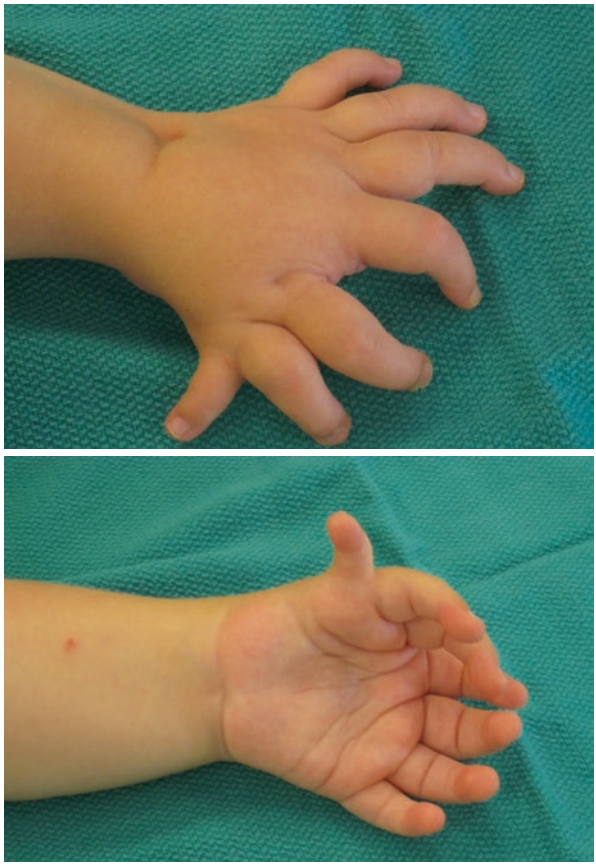


Fig. 12.5 Mirror hand (ulnar dimelia). Note that the hand lacks a functional thumb

Clinical Presentation: History and Physical

Syndactyly

Syndactyly is defined as simple if there is fusion of soft tissue components only, and complex if there is fusion of the bone in addition to the soft tissues. Additionally, syndactyly is considered complete if the finger fusion extends from the hand all the way to the fingertip, and incomplete if the fusion ends proximal to the fingertip. The most common location for syndactyly is between the middle (third) and ring (fourth) fingers (Fig. 12.6). A syndactyly that has additional skeletal anomalies, e.g., abnormally oriented bones, is further classified as complicated. Acrosyndactyly is a type of syndactyly in which there is fusion at the distal ends of the finger but with fenestration proximally. Acrosyndactyly is most commonly seen in amniotic band syndrome and Apert syndrome (acrocephalosyndactyly).

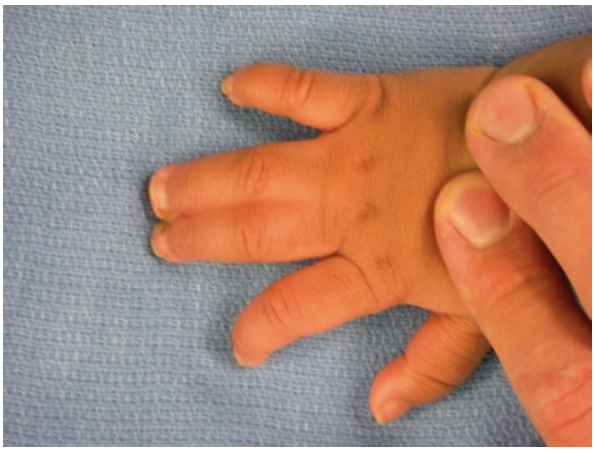


Fig. 12.6 Simple complete polydactyly between the middle and ring fingers

Evaluation

Both polydactyly and syndactyly of the hand are typically identified at birth or shortly thereafter. When these anomalies are present, special attention should be paid to look for other congenital abnormalities that would suggest the presence of a syndrome. There is no immediate urgency during the postnatal period to obtain radiographs of the affected hand, since surgery is generally deferred until after 6 months of age. During subsequent evaluation by the hand surgeon, radiographs will be obtained in order to delineate the skeletal anatomy. This information will aid in surgical planning and the determination of prognosis.

Management

In general, most congenital polydactyly and syndactyly problems can be managed surgically to improve hand function and appearance. Surgical procedures can vary from simple to complex reconstructions, depending on the complexity of the abnormal anatomy. Although timing for surgical intervention is a matter of surgeon preference, most surgeons recommend performing surgery for these conditions when the child is 6 to 18 months of age. Timing considerations include anesthesia safety, size of the hand, and developmental milestones. The risks of anesthesia-related complications decrease greatly after the child is 6 months old. For the more complex cases, multiple surgical procedures spread over many months or years may be recommended.

Due to its importance in normal hand function, radial (thumb) polydactyly reconstruction is recommended in virtually every case. The surgical goal is to create the best functioning thumb possible by utilizing components of both thumbs. Often this means using components of the most hypoplastic thumb to augment those of the more normal retained thumb. Surgical techniques include ligament reconstruction, transfer of the intrinsic hand muscles to the preserved digit, and reinforcement of the extrinsic flexor and extensor tendons.

In the treatment of ulnar polydactyly, ligation, or "tying off," in the newborn nursery of some type B ulnar polydactylies is feasible if there is a small, underdeveloped digit connected by a narrow soft tissue stalk. Ligation causes necrosis and eventual auto-amputation of the nubbin. Parents should be advised that it may take 2–4 weeks for the necrotic digit to fall off. However, there are many reports of an unpleasing scar, a small mound of tissue, or painful neuromas following simple ligation. In order to avoid these complications, some physicians no longer routinely recommend ligation of type B polydactylies. Certainly, type B anomalies that have a broad connection are best treated with formal surgical excision in the operating room. Similarly, the more extensive skeletal connection of type A ulnar polydactyly does not lend itself to tying off in the newborn period. Type A ulnar polydactylies are best treated surgically later in infancy.

Central polydactyly is treated by surgical excision of the most hypoplastic digit. When associated with syndactyly, separation of the digit is usually performed concurrently. This can be surgically challenging. Underlying bone and joint abnormalities may cause decreased joint mobility and abnormal alignment after otherwise successful surgery. If the central supernumerary digit is fully developed and has normal function, non-surgical observation can be considered.

In cases of mild incomplete simple syndactyly, surgery may not be necessary. For those syndactylies that do require surgery, better outcomes have been reported when syndactyly surgery is performed after 18 months of age [8]. The larger hand size compared to the younger child makes the technical aspects of the surgery easier. When surgery is performed in patients younger than 18 months of age, there is a greater risk for the development of post-surgical web creep as the child grows. Web creep is the undesired process in which the commissure between the fingers is drawn over time in a distal direction by scar contraction.

In cases in which syndactylies span multiple contiguous digits, surgical reconstruction should be performed in multiple stages (Fig. 12.7). The digital blood vessels course along the ulnar and radial sides of each finger. A basic principle of hand surgery is the avoidance of operating on both sides of a finger at a single surgical encounter. Instead, separating surgeries by at least 3 months allow collateral

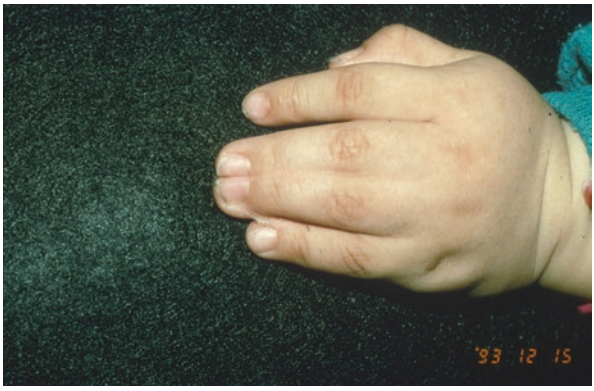


Fig. 12.7 Syndactyly between the middle and ring fingers (complete complex) and between the ring and small fingers (complete simple). Surgical correction was performed in two stages in order to minimize the risk of vascular compromise to the ring finger

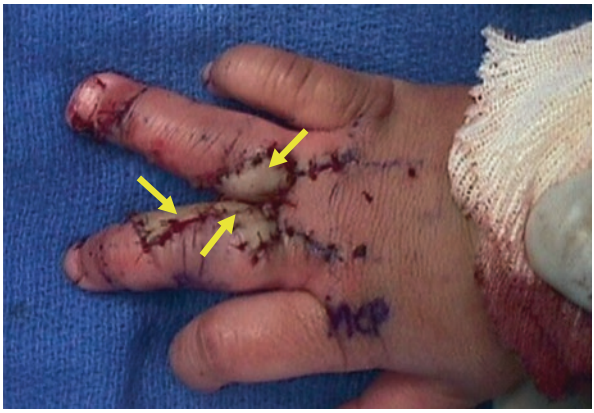


Fig. 12.8 Patient from Fig. 12.6. Surgical separation was performed at 16 months of age. Because of the greater surface area after finger separation, full thickness skin graft was placed during closure (yellow arrows)

circulation and revascularization to occur, and thus minimizes the risk of vascular compromise and iatrogenic necrosis. The goal is to complete all stages of surgery by school age.

When syndactyly surgery is performed, full thickness skin grafting is usually required (Fig. 12.8). This is because the surface area of the skin around conjoined fingers is less than the surface area of skin needed to cover the fingers once they are separated. Skin grafting fills the deficit.

Clinical Pearls

Polydactyly

- Polydactyly may be isolated disorder or an element of a syndrome.
- The most common forms of polydactyly are radial polydactyly and ulnar polydactyly.
- Radial polydactyly resembles thumb duplication or split thumb.
- Only the most rudimentary polydactyly should be considered for tying off in the newborn period. Complications of tying off including an undesirable scar, a mound of tissue, and/or a painful neuroma.
- Most polydactylies are removed surgical after 6 months of age.

Syndactyly

- Syndactyly may be isolated or an element of a syndrome.
- Syndactyly is described as simple vs. complex, complete vs. incomplete, or complicated.

- The most common location for syndactyly is between the middle and ring fingers.
- Delaying reconstructive surgery to closer to 14 months of age may minimize the complication of web creep.
- If a child has multiple syndactylies, surgical reconstruction will be staged.
- Virtually every syndactyly surgery will require skin grafting to cover skin deficits.

References

1. Ho C. Chapter 15: Disorders of the upper extremity. In: Tachdjian's pediatric orthopaedics: from the Texas Scottish Rite Hospital for Children. 5th ed. Dallas: Elsevier; 2014. p. 388–452.
2. Malik S. Polydactyly: phenotypes, genetics and classification. Clin Genet. 2014;85(3):203–12.
3. Deng H, Tan T, Yuan L. Advances in the molecular genetics of non-syndromic polydactyly. Expert Rev Mol Med. 2015;17:e18.
4. Ahmed H, Akbari H, Emami A, Akbari MR. Genetic overview of syndactyly and polydactyly. Plast Reconstr Surg Glob Open. 2017;5(11):e1549.
5. Wassel HD. The results of surgery for polydactyly of the thumb: a review. Clin Orthop Relat Res. 1969;64:175–93.
6. Wood VE. Treatment of central polydactyly. Clin Orthop Relat Res. 1971;74:196–205.
7. Tada K, Kurisaki E, Yonenobu K, Tsuyuguchi Y, Kawai H. Central polydactyly: a review of 12 cases and their surgical treatment. J Hand Surg Am. 1982;7(5):460–5.
8. Kay SP, McCombe DB, Kozin SH. Chapter 36: Deformities of the hand and fingers. In: Green's operative hand surgery. 7th ed. Philadelphia: Elsevier; 2017. p. 1217–32.

Suggested Readings/Additional Resources

Baek GH, Gong HS, Chung MS, Oh JH, Lee YH, Lee SK. Modified Bilhaut-Cloquet procedure for Wassel type-II and III polydactyly of the thumb. J Bone Joint Surg Am. 2007;89(3):534–41.

Canizares MF, Feldman L, Miller PE, Waters PM, Bae DS. Complications and cost of syndactyly reconstruction in the united states: analysis of the pediatric health information system. Hand (New York, NY). 2017;12(4):327–34.

Comer GC, Potter M, Ladd AL. Polydactyly of the hand. J Am Acad Orthop Surg. 2018;26(3):75–82.

Dao KD, Shin AY, Billings A, et al. Surgical treatment of congenital syndactyly of the hand. J Am Acad Orthop Surg. 2004;12:39–48.

Holmes LB, Nasri H, Hunt AT, Toufaily MH, Westgate MN. Polydactyly, postaxial, type B. Birth Defects Res. 2018;110(2):134–41.

Kozin SH, Zlotolow DA. Common pediatric congenital conditions of the hand. Plast Reconstr Surg. 2015;136(2):241e–57e.

Malik S. Syndactyly: phenotypes, genetics and current classification. Eur J Human Genet. 2012;20(8):817–24.

Perez-Lopez LM, la Iglesia DG, Cabrera-Gonzalez M. Radial polydactyly. What's new? Curr Pediatr Rev. 2018;14(2):91–6.

Temtamy SA, McKusick VA. The genetics of hand malformations. Birth Defects Orig Artic Ser. 1978;14(3):i–xviii, 1–619.

Winter RM, Tickle C. Syndactylies and polydactylies: embryological overview and suggested classification. Eur J Human Genet. 1993;1(1):96–104.

Chapter 13
Trigger Thumb

Mia M. Qin and Richard W. Nicolay III

Background

Pediatric trigger thumb is caused by a developmental size mismatch between the flexor pollicis longus tendon and its sheath. It results in a flexion deformity of the thumb interphalangeal joint. Characteristically, a nodule is palpable on the tendon near the metacarpal phalangeal joint. Definitive treatment of pediatric trigger thumb is surgery, but observation and splinting may play a part as well.

Epidemiology/Pathophysiology

The true incidence of pediatric trigger thumb is unknown, but it is thought to be between 1 and 3 in 1000 [1, 2]. Historically, pediatric trigger thumb was thought to be congenital; however, multiple studies suggest that it is acquired [3–6]. It is not believed to be genetic, but there have been some reports documenting autosomal dominant inheritance with variable penetrance [7].

The etiology of trigger thumb in children is not known. There is an anatomical mismatch between the diameter of the tendon sheath and the diameter of the flexor pollicis long tendon resulting in abnormal gliding of the flexor pollicis longus tendon at the A1 pulley (Fig. 13.1). The exact pathophysiology is unknown, but some studies suggest that a constant flexed position of the thumb during the prenatal and neonatal period results in collagen degeneration and synovial proliferation. This then leads to a nodule in the flexor pollicis longus tendon, referred to as Notta's nodule after first being recognized by Alphonse Henri Notta in 1850 [8] and

M. M. Qin (✉) · R. W. Nicolay III
Department of Orthopedic Surgery, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA
e-mail: richard.nicolay@northwestern.edu

J. F. Sarwark, R. L. Carl (eds.), *Orthopaedics for the Newborn and Young Child*,
https://doi.org/10.1007/978-3-031-11136-5_13

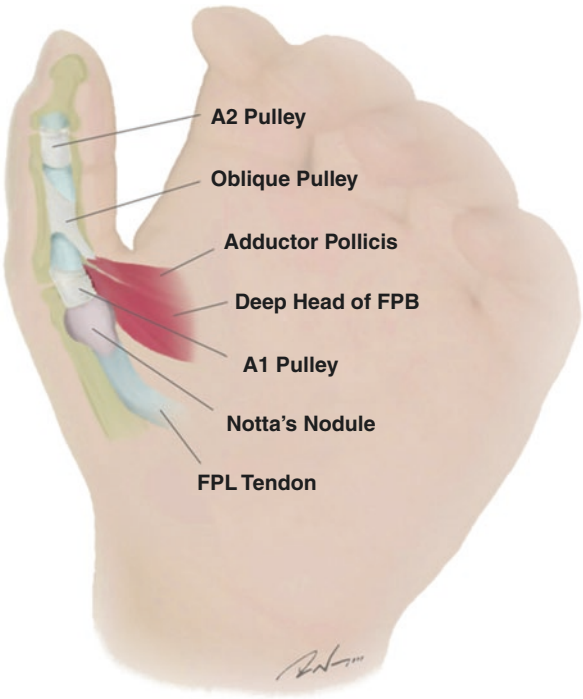


Fig. 13.1 Trigger thumb anatomy

thickening of the tendon sheath [9, 10]. Analysis of the Notta's nodule and the A1 pulley reveal that there are large amounts of mature collagen and fibroblasts but no degenerative or inflammatory changes in the tendon or sheath [11].

Common Clinical Presentation

Most children present between age 1 and 4, most commonly around 2 years of age [5, 11, 12]. 25% of children have bilateral symptoms, but both sides generally do not begin triggering at the same time [1, 12]. Children can present with the thumb locked in flexion or with difficulty flexing and extending the thumb (Fig. 13.2). There is occasionally a preceding history of trauma, which is likely what causes the caregiver or clinician to notice the trigger thumb. Sometimes children are referred to evaluate for interphalangeal joint dislocation or fracture [1]. Generally, it is painless, but some children may have pain with forced extension of the thumb.

On physical exam, children can have difficulty with and experience snapping during extension of the interphalangeal joint of the thumb or can have a fixed flexion deformity of the interphalangeal joint. They have a palpable volar mass at the metacarpal phalangeal joint, referred to as Notta's nodule. The diagnosis is made clinically and does not require radiographic evaluation.

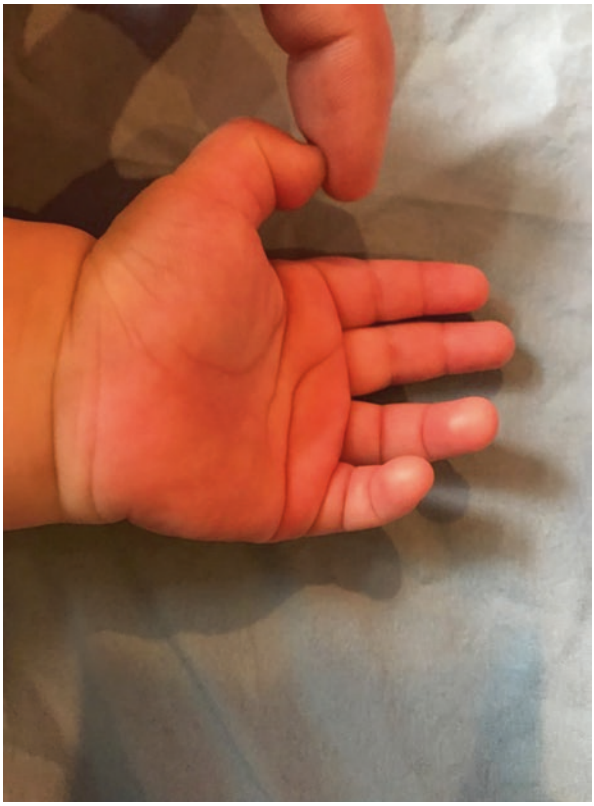


Fig. 13.2 Fixed flexion deformity of interphalangeal joint

Treatment/Management

Treatment options include both nonsurgical and surgical. Nonsurgical treatment options include observation, stretching, and splinting. With observation alone, the rate of spontaneous resolution rate was 12% after 6 months [1] and 63% after 48 months [13]. If substantial improvement was not seen after 2 years of observation, the benefit of continued observation was limited. Passive extension exercises have not been largely shown to be helpful. In 48 children with 60 trigger thumbs, motion remained abnormal in 59% after passive stretching [14]. Extension splinting is also an option, but again, is not universally successful. In 40 trigger thumbs treated with dorsal extension splinting worn at night and during naps for an average of 10 months, only 60% had full resolution of the trigger thumb [15]. Other studies have found some improvement in thumb interphalangeal joint extension, but normal motion only restored in 39% of splinted thumbs [16]. Observation alone has similar success rates to stretching and splinting. It is reasonable to consider non-operative management in trigger thumbs without a fixed flexion deformity. However, in those fixed in flexion, observation, extension exercises, or splinting is unlikely to yield success.

Open surgical release of the A1 pulley of the thumb is effective in restoring interphalangeal joint motion with minimal risk of neurovascular injury, infection, and persistent or recurrent triggering [1, 4, 5, 9, 12]. The recurrence rate is approximately 4%, however patients under 36 months of age may be at higher risk of recurrence [17]. The age at which surgery should be performed is not well known. There is low risk for persistent joint contracture if surgery is delayed. In children with mean age of 7.5 years, all interphalangeal joint contractures were resolved by 8 weeks post-operatively [18]. Percutaneous techniques have been described to release the A1 pulley; however, these have a higher recurrence rate at 10% [19].

The surgery is performed under general anesthesia, in the supine position, with the arm supported by a hand table. A 1 cm transverse incision is made at the thumb metacarpal phalangeal flexion crease, which is centered over the A1 pulley. Using blunt dissection, the flexor tendon sheath is exposed. The digital arteries and nerves need to be protected with gentle retraction. Under direct visualization, the A1 pulley is sharply incised. The proximal edge of the oblique pulley should be identified and preserved. After the A1 pulley is released, the Notta's nodule can easily be identified. During passive IP joint extension, the flexor pollicis longus should be examined as it glides smoothly without triggering. After the skin is closed, a bulky dressing should be applied. Children do not require hand therapy post-operatively [20].

Current References Including Applicable Position Statements

The American Academy of Orthopedic Surgeons (AAOS) recommends surgical release in patients with fixed flexion contractures who are older than 12 months due to the prolonged period of time associated with nonsurgical management. Observation may be pursued if the caretaker prefers nonsurgical management because there is no evidence that links the duration of symptoms with post-operative loss of interphalangeal motion. However, the AAOS recommends discontinuing nonsurgical measures after 2 years because the potential for spontaneous recovery beyond this period is limited. Regarding surgical technique, the AAOS favors open over percutaneous A1 pulley release to minimize iatrogenic injury to the digital nerves and minimize risk of recurrence due to incomplete A1 pulley release [20].

References

1. Dinham JM, Meggitt BF. Trigger thumbs in children. A review of the natural history and indications for treatment in 105 patients. J Bone Joint Surg Br. 1974;56(1):153–5.
2. Steenwerckx A, De Smet L, Fabry G. Congenital trigger digit. J Hand Surg Am. 1996;21(5):909–11.
3. Rodgers WB, Waters PM. Incidence of trigger digits in newborns. J Hand Surg Am. 1994;19(3):364–8.

4. Moon WN, Suh SW, Kim IC. Trigger digits in children. J Hand Surg Br. 2001;26(1):11–2.
5. Slakey JB, Hennrikus WL. Acquired thumb flexion contracture in children: congenital trigger thumb. J Bone Joint Surg Br. 1996;78(3):481–3.
6. Kikuchi N, Ogino T. Incidence and development of trigger thumb in children. J Hand Surg Am. 2006;31(4):541–3.
7. Shim VC, Admire AA, Heidenreich RA, Samimi KJ. Autosomal dominant inheritance pattern for trigger thumb. Plast Reconstr Surg. 2002;109(1):240–1. discussion 2.
8. Clapham PJ, Chung KC. A historical perspective of the Notta's node in trigger fingers. J Hand Surg Am. 2009;34(8):1518–22.
9. Sprecher EE. Trigger thumb in infants. J Bone Joint Surg Am. 1949;31A(3):672–4.
10. Fahey JJ, Bollinger JA. Trigger-finger in adults and children. J Bone Joint Surg Am. 1954;36-A(6):1200–18.
11. Buchman MT, Gibson TW, McCallum D, Cuda DD, Ramos AG Jr. Transmission electron microscopic pathoanatomy of congenital trigger thumb. J Pediatr Orthop. 1999;19(3):411–2.
12. Marek DJ, Fitoussi F, Bohn DC, Van Heest AE. Surgical release of the pediatric trigger thumb. J Hand Surg Am. 2011;36(4):647–52 e2.
13. Baek GH, Kim JH, Chung MS, Kang SB, Lee YH, Gong HS. The natural history of pediatric trigger thumb. J Bone Joint Surg Am. 2008;90(5):980–5.
14. Watanabe H, Hamada Y, Toshima T. Conservative management of infantile trigger thumb: indications and limitations. Tech Hand Up Extrem Surg. 2003;7(1):37–42.
15. Nemoto K, Nemoto T, Terada N, Amako M, Kawaguchi M. Splint therapy for trigger thumb and finger in children. J Hand Surg Br. 1996;21(3):416–8.
16. Lee ZL, Chang CH, Yang WY, Hung SS, Shih CH. Extension splint for trigger thumb in children. J Pediatr Orthop. 2006;26(6):785–7.
17. Dunsmuir RA, Sherlock DA. The outcome of treatment of trigger thumb in children. J Bone Joint Surg Br. 2000;82(5):736–8.
18. Han SH, Yoon HK, Shin DE, Song DG. Trigger thumb in children: results of surgical treatment in children above 5 years of age. J Pediatr Orthop. 2010;30(7):710–4.
19. Wang HC, Lin GT. Retrospective study of open versus percutaneous surgery for trigger thumb in children. Plast Reconstr Surg. 2005;115(7):1963–70. discussion 71–2.
20. Shah AS, Bae DS. Management of pediatric trigger thumb and trigger finger. J Am Acad Orthop Surg. 2012;20(4):206–13.

Chapter 14
Congenital Scoliosis

Eric B. Fuller

Brief Overview of Condition

Congenital scoliosis accounts for 10% of all pediatric spinal deformities [1, 2]. It is caused by an abnormality of the vertebrae of the spine, occurring during fetal development. It often presents in the first few years of life. Once congenital scoliosis is identified, it is important for the clinician to rule out other medical conditions that are associated with it. Treatment of congenital scoliosis includes determining the risk of curve progression and implementing the appropriate care based on progression.

Background Including Epidemiology and Pathophysiology

The prevalence of congenital vertebral anomalies is estimated to be 0.5–1/1000 births [1, 3, 4]. Since not all vertebral anomalies progress to clinical scoliosis, this number is likely under-reported. Congenital anomalies of the spine occur during the fourth to sixth week of embryogenesis by genetic and/or environmental factors [5]. Genetic predilection for congenital scoliosis is typically associated with multiple system abnormalities or syndromes and is sporadic (non-genetic) although a family history of scoliosis [6] and the risk of subsequent siblings having scoliosis is minimal [3]. As genetics alone does not usually cause congenital defects in the spine, environmental factors such as exposure in a susceptible individual can cause it. Known environmental causes of congenital scoliosis are maternal diabetes, hypoxia, carbon monoxide, cigarette smoking, ethanol, vitamin A deficiency, retinoic acid,

E. B. Fuller (✉)
Department of Orthopaedic Surgery, Ann & Robert H. Lurie Children's Hospital, Chicago, IL, USA
e-mail: efuller@luriechildrens.org

J. F. Sarwark, R. L. Carl (eds.), *Orthopaedics for the Newborn and Young Child*,
https://doi.org/10.1007/978-3-031-11136-5_14

hyperthermia, and valproic acid [7]. Local factors such as twinning or fetal compression are also causative.

The vertebral anomaly morphologies that cause congenital scoliosis are classified either as a failure of segmentation between the vertebral bodies or a failure of formation of the vertebral bodies themselves [8] or a mixed form which occurs 20% of the time [9].

A failure of segmentation, or separation, between the vertebral bodies may cause an abnormal bony bar between adjacent vertebra [10]. These abnormal connections cause an asymmetric lack of disc space and growth plates between the two vertebra. If the fusion occurs across the entire width of the vertebra, this is known as a block vertebra and this is not likely to cause scoliosis (Fig. 14.1a). If a unilateral bar forms, the lack of growth on one side of the vertebra causes the spine to curve with growth of the contralateral side (Fig. 14.1b). Accordingly, the unilateral unsegmented bar is located on the concave side of the curve.

A failure of formation of the vertebral bodies causes the normally rectangular vertebra, when viewed in the coronal plane, to appear triangular (Fig. 14.2a, b). These types of defects cause scoliosis either wedge vertebra or hemivertebra or

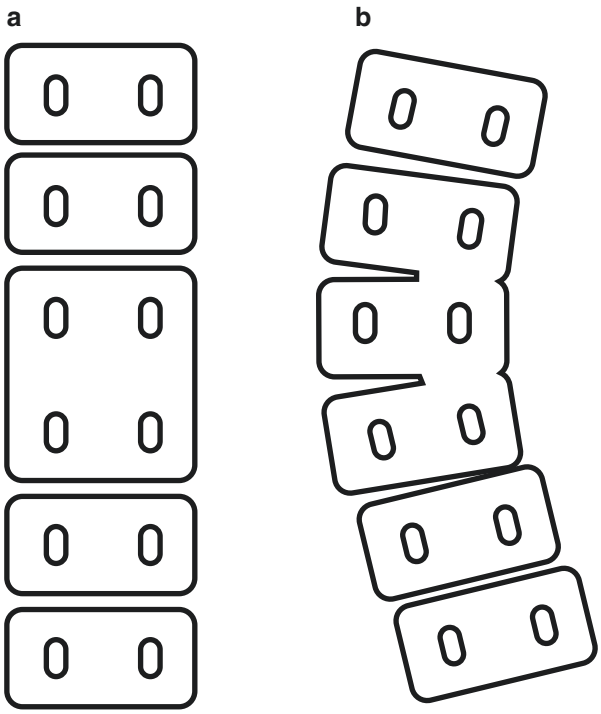


Fig. 14.1 Failure of segmentation. (**a**) Block vertebra. (**b**) Unilateral bar formation

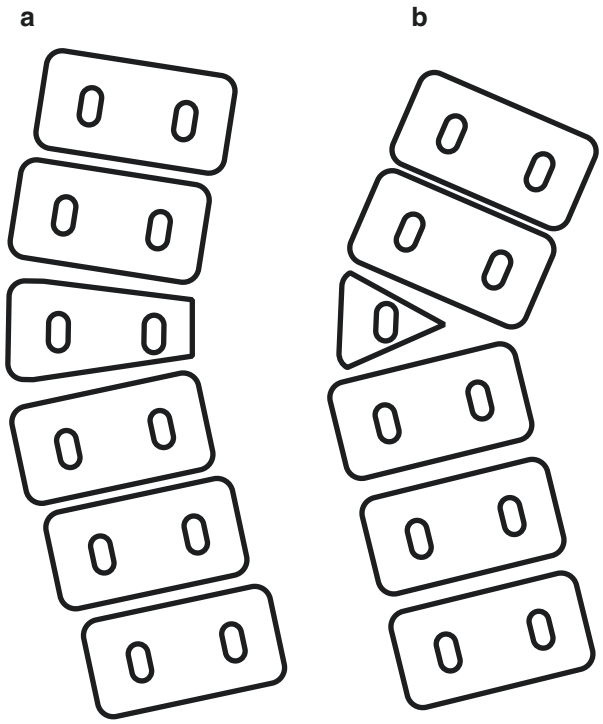


Fig. 14.2 Failure of formation. (**a**) Wedge vertebra. (**b**) Hemivertebra

butterfly vertebra [11]. A wedge vertebra is differentiated from a hemivertebra by the number of pedicles the vertebra has. A wedge vertebra crosses the midline of the spine and has two pedicles (Fig. 14.2a) caused by an incomplete formation of one side of the vertebra, resulting in an asymmetrical decrease in vertebral height; the shorter side of the vertebra lies on the concave side of the curve. A hemivertebra does not cross the midline and has only a single pedicle (Fig. 14.2b); it may be an extra half of a vertebra on the convex side of the spine, complete with an extra rib if in the thoracic spine, or a complete absence of half a vertebra on the concave side, resulting in one less rib on that side. The presence of a hemivertebra portends a higher risk of curve progression than a wedge vertebra [11].

Mixed lesions occur in many patients with congenital scoliosis [9]. A hemivertebra may be fully segmented, semi-segmented, or incarcerated (non-segmented) (Fig. 14.3a, b). The more segmented the hemivertebra is, the more growth potential it has. This correlates to a higher risk of curve progression. A unilateral bar with a contralateral fully segmented hemivertebra carries the highest risk of curve progression and almost always necessitates surgical management (fusion) [12] (Fig. 14.4).

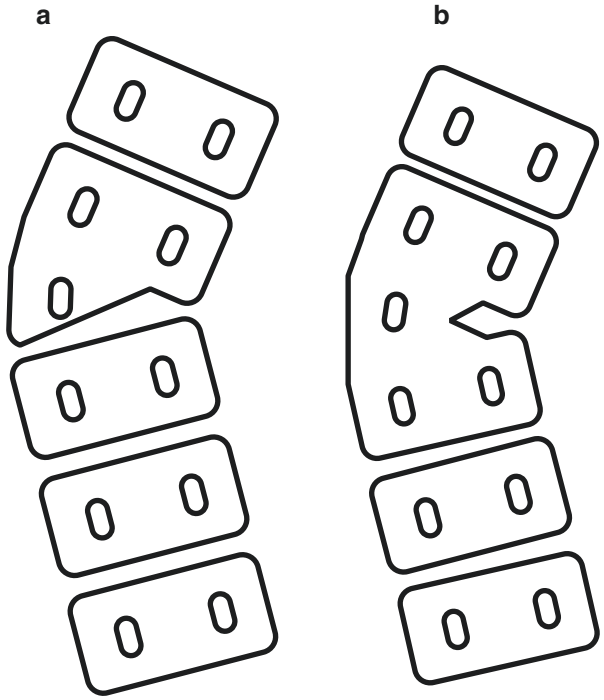


Fig. 14.3 Mixed anomalies. (**a**) Hemivertebra with partial segmentation. (**b**) Unsegmented hemivertebra

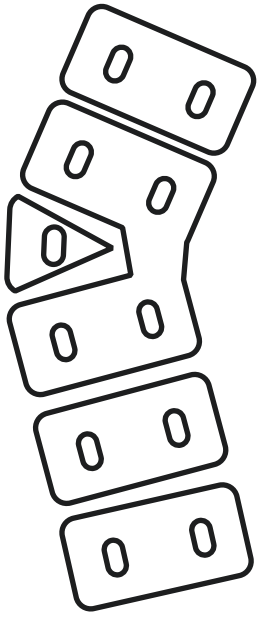


Fig. 14.4 Unilateral bar with a contralateral fully segmented hemivertebra

Clinical Presentation: History and Physical

Congenital scoliosis is usually diagnosed within the first 3 years of life upon routine physical examination or incidentally found on imaging obtained for other causes, such as a chest X-ray for a respiratory infection [1]. However, it may be found as early as the 20-week prenatal ultrasound or as late as the pubertal growth spurt [13]. Because vertebral anomalies occur at a sensitive time in embryologic development, congenital defects of other organ systems are common: The spine develops at the same time as the cardiovascular and genitourinary systems, so anomalies in these systems are often concurrent [14]. Additionally, there are over 40 non-genetic syndromes identified that are associated with vertebral anomalies [15], including VACTERL syndrome—vertebral anomalies, anal atresia, cardiovascular anomalies, tracheoesophageal fistula, and limb anomalies. Therefore, a comprehensive examination should be performed when congenital scoliosis is first diagnosed.

The history should include the prenatal and birth periods to look for environmental causes and should also include a family history. The previous growth charts should be reviewed to predict future growth remaining.

The physical exam findings that most commonly predict vertebral anomalies before congenital scoliosis is apparent are asymmetric abdominal reflexes and neurocutaneous stigmata. A comprehensive physical exam to look for possible vertebral anomalies should include a thorough neurological assessment of motor strength, sensation, and reflexes. Associated spinal cord anomalies with neurologic manifestations occurs 4–36% of the time [16]. The exam should also include a head-to-toe skin examination to look for café-au-lait spots, axillary freckles, neurofibromas, midline patches of hair, hypertrichosis, dermal sinus tracts, hemangiomas, lumbar dimples, pigmented nevi, subcutaneous lipomas, and telangiectasias [1]. If the patient has progressed to clinically apparent congenital scoliosis, it may be seen upon evaluating the back, manifesting in truncal imbalance on standing, unlevel shoulders or pelvis, or increased truncal rotation on Adam's forward bend test. The positive predictive value of the physical exam or history to detect an intraspinal anomaly is approximately 74%, whereas the negative predictive value is 72% [17].

Once the diagnosis of congenital scoliosis has been suspected or confirmed, the physical exam should proceed with review of systems evaluation of the heart, lungs, chest wall, gastrointestinal and genitourinary systems, and limbs. The heart is known for concurrent primary anomalies, such as ventral septal defects (occurs in 18–26% of children with vertebral anomalies). Additionally, higher magnitude spinal deformities may cause chest wall deformities that compress the thoracic viscera and cause secondary cardiopulmonary pathology, a process called thoracic insufficiency syndrome. The decreased space in the thoracic cavity may cause restrictive lung disease in older children [18] and can decrease lung development and overall lung size in children under the age of 8 [19, 20]. Severe spinal curvature may impact motility of the gastrointestinal tract. Lastly, genitourinary abnormalities are diagnosed in 20–40% of children with vertebral anomalies [14] although renal function is rarely impaired.

Evaluation

Scoliosis of any type suspected on history or physical exam requires a posterior-anterior standing and lateral standing TL-Spine X-ray [15]. The Cobb angle is measured on the posterior-anterior X-ray by measuring the maximum angle between the upper endplate of the upper vertebra and lower endplate of the lower vertebrae [21]. Curves less than 10° are termed minor spinal asymmetry and are considered normal. Curves greater than 10 are termed scoliosis. However, any vertebral anomaly identified on X-ray has the potential to increase in severity with growth of the patient and should be followed at 3–6 month intervals. X-ray is the imaging of choice for surveillance [22]. Referral to an orthopedic surgeon is appropriately recommended for curves over 10° or any vertebral anomaly, regardless of curve severity.

Evaluation for the association of cardiac and genitourinary anomalies should be performed on the heart and kidneys. Echocardiogram is the cardiac imaging modality of choice although MR angiography may be utilized [23]. Renal ultrasound is sufficient to rule out most anatomic renal pathologies [19]. However, if the patient is already undergoing MRI for the scoliosis, the kidneys may be visualized in that field of view.

An MRI of the entire spine from the occiput to the coccyx should be obtained prior to school years to look for associated intraspinal pathology [19]. Any intraspinal lesion should be referred to a neurosurgeon. A CT scan to better define the bony anatomy may be obtained, but may be deferred until surgical treatment is being considered.

Management

The first step in treatment is determining the risk of curve progression. Block or butterfly vertebra and a wedge hemivertebra pose little risk for curve progression and may be watched over time. Additionally, a semi-segmented or incarcerated hemivertebra also may not require intervention [24]. A fully segmented hemivertebra or a unilateral bar carries a moderate risk for curve progression [12] and may require treatment. A unilateral bar with a contralateral fully segmented hemivertebra carries the highest risk of curve progression [12] and frequently requires surgical treatment.

Conservative treatment in congenital scoliosis is observation. Although vitamin D and calcium supplementation is often advised in idiopathic scoliosis, the use in congenital scoliosis has not been studied. Bracing has not been found to be effective for congenital scoliosis, as the curve typically is not flexible [10]. Serial casting or bracing may be used to delay surgical treatment if the patient is young [25–27].

Up to 75% of patients with congenital scoliosis will have progressive curves that require surgical treatment [12]. Indications for surgery are (1) progressing curves over 40–50°, (2) curves that have shown progression on follow-up, (3) curves that are at high risk for progressing [1]. Curves that are at high risk for progression are those with unilateral unsegmented bar, a fully segmented hemivertebra, or both. Partially segmented hemivertebra are a moderate risk for progression, and clinical judgment should be used to determine if observation or surgery is necessary.

Patients requiring surgery can be divided in to 3 groups, and different surgical options exist for each group. The first group is young patients with a lot of growth remaining (typically below age 10) that have short curves (less than five levels). The second group is young patients with long curves. The third group is older patients without much growth remaining.

For young patients having a short curve, surgical options include in situ spinal fusions with or without hemivertebra resection and guided growth with hemiepiphysiodesis of the convex side of the spine [1]. If the curve is less than 40° and is contained in a short segment of spine, then in situ spinal fusion over that short segment is acceptable [28]. The short fusion minimally impacts growth of the remaining spine and chest cavity. Instrumentation of the spine during fusion allows modest reduction of the curve with acceptable low risk [29]. If the curve is over 40°, the curve should be further reduced by performing a hemivertebrectomy if present. Other options include removing the disc and growth plate on the convex side of the curve to arrest its growth and allow the growth on the concave side of the curve to straighten the spine with growth. However, indications for this are limited to children less than 5 years of age, less than 70° of scoliosis, and fully segmented failure of formation anomalies [30], such that sufficient growth exists on the concave side of the curve.

For very young patients with a long curve, a long early fusion is not recommended. Fusing a long segment of the spine can impact the growth of the spine, chest wall, and lungs and can further worsen thoracic insufficiency syndrome [28]. Surgical options for this group of patients must preserve growth of the spine. This includes performing limited, short fusions and using instrumentation that can cause or direct growth. Growing rods are used to actively cause growth. They may be mechanical, which require frequent reoperations to lengthen the rods, or magnetically controlled (an evolving technology) [31]. Guided growth systems allow for passive growth of the spine and have a high complication rate. Another growth-friendly technique includes a vertical expandable prosthetic titanium rib (VEPTR), an implant attaching to the ribs and has the benefit of increasing thoracic volume and preserving the spinal anatomy for later fusion [32]. However, it also has the highest complication rate of all the growth-friendly techniques.

For older patients, performing a long instrumented fusion is preferred. In rare certain circumstances performing, a hemivertebrectomy or vertebral column resection is indicated.

Clinical Vignettes/Clinical Pearls

- Congenital spine deformity occurs during the fourth to sixth weeks of gestation—the same time as the cardiac and renal systems are forming. Accordingly, there is a high association with heart and kidney anomalies that should be evaluated when congenital scoliosis is identified.
- Standing X-rays are the imaging modality of choice for screening and follow-up. In addition to ultrasound for evaluating the heart and kidneys, an MRI should be performed for the entire spine to assess for intraspinal lesions. A CT may also be necessary for surgical planning.
- Scoliosis progresses with growth. Therefore, it is often identified during the first growth spurt, before the age of 3. The younger the patient is when the curve is clinically evident, the higher the risk of it progressing with continued growth. The velocity of curve progression is highest with the pubertal growth spurt.
- Congenital scoliosis has a moderate likelihood of being progressive and requiring treatment. Conservative treatment is limited, as bracing has not been found to be effective in stiff curves.
- The curvature of the spine at a young age negatively affects pulmonary development. Spinal fusion at a young age restricts spinal growth which negatively affects pulmonary development. Therefore, goals of treatment must include reducing thoracic curves while allowing growth of the spine to maximize lung development.
- For young patients with short curves, limited spinal fusion may be performed.
- For young patients with long curves, growth-friendly techniques must be utilized. The complication rate of these techniques varies but all are higher than standard instrumented fusions.
- For older patients, a spinal fusion that addresses the entire deformity is appropriate.

References

1. Mackel CE, Jada A, Samdani AF, Stephen JH, Bennett JT, Baaj AA, Hwang SW. A comprehensive review of the diagnosis and management of congenital scoliosis. Childs Nerv Syst Childs Nerv Syst. 2018;34(11):2155–71. https://doi.org/10.1007/s00381-018-3915-6.
2. Birnbaum K, Weber M, Lorani A, Leiser-Neef U, Niethard FU. Prognostic significance of the Nasca classification for the long-term course of congenital scoliosis. Arch Orthop Trauma Surg. 2002;122(7):383–9.
3. Wynne-Davies R. Congenital vertebral anomalies: aetiology and relationship to spina bifida cystica. J Med Genet. 1975;12(3):280–8.
4. Giampietro PF, Blank RD, Raggio CL, et al. Congenital and idiopathic scoliosis: clinical and genetic aspects. Clin Med Res. 2003;1:125–36.
5. Giampietro PF, Raggio CL, Blank RD, McCarty C, Broeckel U, Pickart MA. Clinical, genetic and environmental factors associated with congenital vertebral malformations. Mol Syndromol. 2013;4(1–2):94–105.

6. Purkiss SB, Driscoll B, Cole WG, Alman B. Idiopathic scoliosis in families of children with congenital scoliosis. Clin Orthop Relat Res. 2002;401:27–31.
7. Alexander PG, Tuan RS. Role of environmental factors in axial skeletal dysmorphogenesis. Birth Defects Res C Embryo Today. 2010;90:118–32.
8. Jaskwhich D, Ali R, Patel T, Green DW. Congenital scoliosis. Curr Opin Pediatr. 2000;12(1):61–6.
9. Pahys JM, Guille JT. What's new in congenital scoliosis? J Pediatr Orthop. 2018;38:e172–9.
10. Hedequist D, Emans J. Congenital scoliosis. J Am Acad Orthop Surg. 2004;12:266–75.
11. McMaster MJ, Singh H. Natural history of congenital kyphosis and kyphoscoliosis. A study of one hundred and twelve patients. J Bone Joint Surg Am. 1999;81:1367–83.
12. McMaster MJ, Ohtsuka K. The natural history of congenital scoliosis. A study of two hundred and fifty-one patients. J Bone Joint Surg Am. 1982;64:1128–47.
13. Varras M, Akrivis C. Prenatal diagnosis of fetal hemivertebra at 20 weeks' gestation with literature review. Int J Gen Med. 2010;3:197–201.
14. Basu PS, Elsebaie H, Noordeen MH. Congenital spinal deformity: a comprehensive assessment at presentation. Spine (Phil, PA, 1976). 2002;27(20):2255–9.
15. Giampietro PF, Dunwoodie SL, Kusumi K, Pourquie O, Tassy O, Offiah AC, et al. Progress in the understanding of the genetic etiology of vertebral segmentation disorders in humans. Ann N Y Acad Sci. 2009;1151:38–67.
16. Beals RK, Robbins JR, Rolfe B. Anomalies associated with vertebral malformations. Spine (Phil, PA, 1976). 1993;18:1329–32.
17. Belmont PJ Jr, Kuklo TR, Taylor KF, Freedman BA, Prahinski JR, Kruse RW. Intraspinal anomalies associated with isolated congenital hemivertebra: the role of routine magnetic resonance imaging. J Bone Joint Surg Am. 2004;86:1704–10.
18. Campbell RM Jr, Smith MD, Mayes TC, Mangos JA, Willey-Courand DB, Kose N, et al. The characteristics of thoracic insufficiency syndrome associated with fused ribs and congenital scoliosis. J Bone Joint Surg Am. 2003;85:399–408.
19. Batra S, Ahuja S. Congenital scoliosis: management and future directions. Acta Orthop Belg. 2008;74:147–60.
20. Muirhead A, Conner AN. The assessment of lung function in children with scoliosis. J Bone Joint Surg Br. 1985;67:699–702.
21. Hong JY, Hwang JH, Suh SW, Yang JH, Kim JR, Bae YG. Reliability of coronal curvature measures in premature scoliosis: comparison of 4 methods using inverted digital luminescence radiography. Spine (Phil, PA, 1976). 2015;40:E701–12. https://doi.org/10.1097/brs.0000000000000875.
22. Bernard TN Jr, Burke SW, Johnston CE 3rd, Roberts JM. Congenital spine deformities. A review of 47 cases. Orthopedics. 1985;8:777–83.
23. Chan G, Dormans JP. Update on congenital spinal deformities: preoperative evaluation. Spine (Phil, PA, 1976). 2009;34:1766–74. https://doi.org/10.1097/BRS.0b013e3181ab62d8.
24. McMaster MJ, David CV. Hemivertebra as a cause of scoliosis. A study of 104 patients. J Bone Joint Surg Br. 1986;68:588–95.
25. Baulesh DM, Huh J, Judkins T, et al. The role of serial casting in early-onset scoliosis (EOS). J Pediatr Orthop. 2012;32:658–63.
26. Johnston CE, McClung AM, Thompson GH, et al. Growing Spine Study Group. Comparison of growing rod instrumentation versus serial cast treatment for early-onset scoliosis. Spine Deform. 2013;1(5):339–42.
27. Demirkiran HG, Bekmez S, Celilov R, et al. Serial derotational casting in congenital scoliosis as a time-buying strategy. J Pediatr Orthop. 2015;35:43–9.
28. Vitale MG, Matsumoto H, Bye MR, Gomez JA, Booker WA, Hyman JE, Roye DP Jr. A retrospective cohort study of pulmonary function, radiographic measures, and quality of life in children with congenital scoliosis: an evaluation of patient outcomes after early spinal fusion. Spine (Phil, PA, 1976). 2008;33:1242–9. https://doi.org/10.1097/BRS.0b013e3181714536.

29. Farley FA, Have KL, Hensinger RN, Streit J, Zhang L, Caird MS. Outcomes after spinal fusion for congenital scoliosis: instrumented versus uninstrumented spinal fusion. Spine (Phil, PA, 1976). 2011;36:E112–22. https://doi.org/10.1097/BRS.0B013e3181efaf5c.
30. Walhout RJ, van Rhijn LW, Pruijs JE. Hemi-epiphysiodesis for unclassified congenital scoliosis: immediate results and midterm follow-up. Eur Spine J. 2002;11:543–9.
31. Akbarnia BA, Cheung K, Noordeen H, Elsebaie H, Yazici M, Dannawi Z, Kabirian N. Next generation of growth sparing techniques: preliminary clinical results of a magnetically controlled growing rod in 14 patients with early-onset scoliosis. Spine (Phil, PA 1976). 2013;38:665–70. https://doi.org/10.1097/BRS.0b013e3182773560.
32. Parnell SE, Effmann EL, Song K, Swanson JO, Bompadre V, Phillips GS. Vertical expandable prosthetic titanium rib (VEPTR): a review of indications, normal radiographic appearance and complications. Pediatr Radiol. 2015;45:606–16.

Chapter 15
Infantile Idiopathic Scoliosis

Eric B. Fuller

Brief Overview of Condition

Early onset scoliosis—idiopathic or infantile idiopathic scoliosis—is defined as scoliosis presenting from birth until the age of 3 without a congenital, syndromic, or neuromuscular cause [1–3]. Like congenital scoliosis, the curve may progress in severity as the patient grows and cause severe comorbidities. The curvature of the spine affects lung development of the young child and treatments must allow continued growth of the spine to ensure continued lung development. Unlike congenital scoliosis, there are some patients who may have spontaneous resolution of their scoliosis [4]. Treatment is based on determining which patients' scoliosis will progress or resolve.

Background Including Epidemiology and Pathophysiology

Infantile idiopathic scoliosis makes up about 4% of idiopathic causes of scoliosis. The prevalence is difficult to determine, as the literature is often directed at "early on-set scoliosis," which includes non-idiopathic causes for scoliosis. As the name suggests, there is no clearly defined pathophysiology for the condition. One of the more validated theories is that during growth there is a relative overgrowth of the anterior spine compared to the posterior elements [5]. This initially causes hypokyphosis of the spine. If the overgrowth continues, the spine must rotate and curve to accommodate the excessive height of the vertebral bodies. The trigger for overgrowth of the anterior spine is not known.

E. B. Fuller (✉)
Department of Orthopaedic Surgery, Ann & Robert H. Lurie Children's Hospital, Chicago, IL, USA
e-mail: efuller@luriechildrens.org

J. F. Sarwark, R. L. Carl (eds.), *Orthopaedics for the Newborn and Young Child*,
https://doi.org/10.1007/978-3-031-11136-5_15

Spine growth occurs rapidly before the age of 5 [6, 7]. After age 5, the growth of the spine decelerates until the age of 10 and then accelerates again until skeletal maturity [6] and so, scoliosis is often diagnosed during infancy or adolescence. Accelerated growth during these times also puts the spine at most risk for progressing in curve magnitude.

Growth and development of the alveoli and supporting lungs occur most rapidly before the age of 8 [8, 9]. It is dependent on spine growth to allow sufficient chest cavity space for maturity. Scoliosis identified in infancy may have a negative impact on lung development. It is important to not only treat the scoliosis to allow for maximum lung development, but to do so in a way that still allows spine growth so that lung size is not reduced.

Infantile idiopathic scoliosis is not the same as adolescent idiopathic scoliosis in an infant. Unlike the adolescent variety, it affects males more than females. It also is predominately a left sided thoracic curve as opposed to a right sided curve. The most contrasting feature, however, is that some infantile idiopathic scoliosis may resolve without any treatment [4]. Identifying which patients require treatment and which will resolve requires follow-up for treatment decisions in EOS-I (infantile idiopathic scoliosis).

Clinical Presentation: History and Physical

Idiopathic scoliosis is a diagnosis of exclusion. A complete history and physical should be performed to look for other causes of scoliosis. Congenital, syndromic, and neuromuscular causes of scoliosis should be considered. Table 15.1 includes some common causes of early onset scoliosis. The history should include the prenatal and infant periods. It should also include a family history. Developmental milestones should be assessed, as cognitive delays are a negative predictor for curve

Table 15.1 Common non-idiopathic causes of early onset scoliosis

Congenital
Vertebral anomalies
Chest wall deformities (pectus excavatum, fused ribs)
Syndromic
Connective tissue disorders (Marfan, Ehlers-Danlos, Neurofibromatosis)
Down syndrome
Prune belly syndrome
Prader-Willi
Skeletal dysplasia
Neuromuscular
Cerebral palsy
Intra-spinal pathology (syrinx, tethered cord, tumor)
Spinal muscular atrophy

progression [10, 11]. Previous growth charts should be reviewed to predict future growth remaining.

A comprehensive physical exam to evaluate for scoliosis includes an examination of the back. In a child unable to stand, the practitioner may palpate the spine and look for rib asymmetry. Scoliosis is often identified as a subtle prominence of the ribs on one side of the back [4]. If the patient can stand, the practitioner will assess truncal imbalance, unlevel shoulders or pelvis, or increased truncal rotation on Adam's forward bend test. If scoliosis is observed on exam, an assessment of the flexibility of the curve should be done by holding the patient up by the axilla and seeing if the curve reduces. A rigid curve is more likely to progress than a flexible curve [7].

The exam includes a neurological assessment of motor strength, sensation, and reflexes. Ability to assess motor and sensation is dependent on patient's function. For an infant unable to participate in graded muscle strength testing, one can exam muscle tone, limb symmetry, and assess for proximal weakness by Meryon or Gower signs. For the walking child, gait should be examined. The neurological examination should also include deep tendon reflexes and abdominal reflexes, as well as age-appropriate reflexes such as Moro reflex or Babinski sign. The foot should also be assessed for deformity such as cavus or equinus, as this may often be the only neurological sign that there is an abnormality in the spine [4].

The exam includes a head to toe examination to look for non-idiopathic causes of scoliosis. This includes, but is not limited to, assessing the head and body for pathognomonic features of other syndromes. The skin should be assessed for café-au-lait spots, neurofibromas, sacral dimpling, or hairy patches. The joints should be assessed for hypermobility or spasticity. Evaluation for an association of developmental dysplasia of the hip, inguinal hernia, plagiocephaly, and congenital heart disease in patients with early onset idiopathic scoliosis [10, 11] should be taken into consideration during the exam.

Evaluation

Radiographs should include PA and lateral standing X-rays of the spine. If the patient is unable to stand, a supine AP and lateral X-ray will suffice; it will underestimate the magnitude of the curve. The X-ray should first be evaluated for any congenital abnormalities of the ribs or vertebra. The Cobb angle should then be measured. Cobb angles greater than 20 have a higher risk of progression [12]. If scoliosis is present and determined to be idiopathic, then evaluation of the apical vertebra and its associated ribs is made (Fig. 15.1). If there is overlap of the rib with the vertebra on the AP or PA X-ray, that means there is substantial rotation of the vertebra. This is associated with a high risk of curve progression [12]. If there is no overlap, a measurement of the rib-vertebral angle difference (RVAD) should be made (Fig. 15.2).

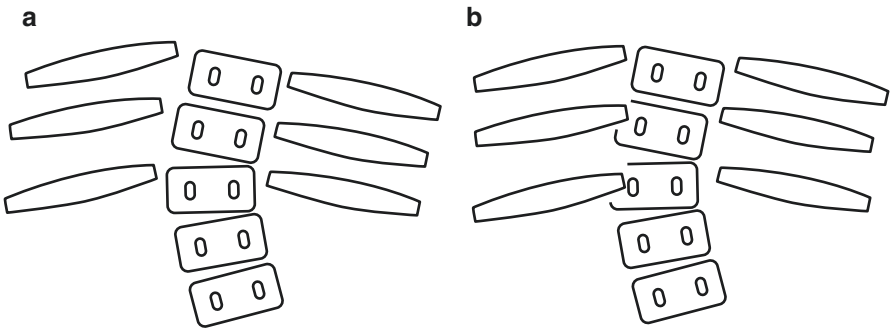


Fig. 15.1 Determining the apical vertebra and rib relationship. (**a**) Phase 1. No overlap of the rib over the vertebral body. (**b**) Phase 2. There is overlap of the rib over the vertebral body, indicating progression of the curve

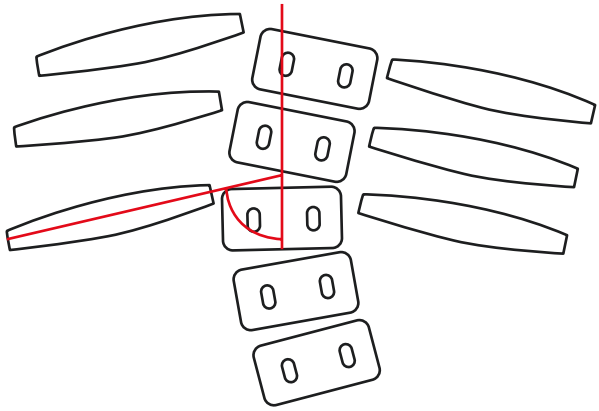


Fig. 15.2 Measuring the rib vertebral angle difference (RVAD)

The RVAD is the difference between the angles each vertebra makes with the apical vertebra. The angle of each rib is determined by a line drawn from the mid-point of the neck of the rib to the mid-point of the rib head and a line drawn perpendicular to the upper or lower border of the vertebral body. Once the rib-vertebra angle is measured for both ribs, the RVAD can be calculated as the difference between the RV angle on the concave side of the curve and the RV angle on the convex side. An RVAD over 20° has a high likelihood of curve progression [12]).

For any neurological abnormalities on exam or curves with a Cobb angle over 20° irrespective of neurological exam, an MRI of the spine is advised. Between 10 and 20% of infants with normal neurological exams and curves over 20° had intraspinal pathology [13], most of which required neurosurgical intervention. Echocardiogram and renal ultrasound are not routinely required, as in congenital scoliosis.

Management

Curves with a Cobb angle less than 20° and/or curves with an apical vertebra that has no overlap of the convex rib and an RVAD less than 20° has a high likelihood of spontaneous resolution. Close observation is recommended.

For curves with a Cobb angle greater than 25°, documented Cobb angle progression of more than 10°, apical vertebra with rib overlap, or a RVAD greater than 20°, treatment is necessary [14]. Observation and non-operative treatment should be tried first. Surgical treatment is reserved for failure of non-operative treatment or curves with a Cobb angle greater than 60°. Non-operative treatment consists of bracing or serial casting.

Bracing has well documented success in adolescent idiopathic scoliosis in maintaining the magnitude of the curve [15]. However, its efficacy in EOS-I (infantile idiopathic scoliosis) remains unclear [4]. Regardless, bracing is being utilized for early onset scoliosis in delaying the need for surgery to allow for further growth of the spine. Bracing has the benefits of being able to be taken off for hygiene; conversely poor patient compliance is a concern. Bracing is typically performed without anesthesia, so less correction can be achieved than with casting. Goals of bracing are to maintain a curve (curve regression is less likely) [4]. If the patient is older, molding of the brace may be performed on a Risser frame table, which allows for more 3-dimensional correction in the brace. Therefore, bracing may be better utilized in older children where curve regression is less likely or to maintain a reduced curve after serial casting.

Serial casting has been shown to reduce the curve to less than 10° in young patients with moderate Cobb angles [16, 17], thus effectively treating scoliosis. Previous Risser casts only provided 2-dimensional correction and were not successful. However, newer techniques that de-rotate the spine in 3 dimensions have been much more successful. The serial casts require general anesthesia and a specialized casting frame for positioning the patient in the operating room. Casts are generally changed every 2–4 months, depending on growth [14]. Although patient compliance is not an issue, casting complications such as pressure sores, loose fitting cast, cast impingement, etc. may make for poor tolerance of the cast.

Surgery is reserved for failure of non-operative treatment, which is defined as curve progression of more than 10–20° in spite of treatment or absolute curve magnitude of 60° [18]. If the patient is over the age of 10 a definitive spinal fusion with instrumentation may be performed; this would not differ from adolescent idiopathic scoliosis. If the patient is under the age of 10, then growth preserving techniques will be utilized. This includes utilizing active growing rods, either mechanical or magnetically lengthened, utilizing passive growth guidance techniques, using VEPTR rods, or utilizing guided growth of the spine [18]. These various techniques were discussed in the previous chapter on congenital scoliosis. These techniques act to allow growth and maintain alignment of the spine until a definitive fusion can be performed at a later age. They do not replace the need for definitive fusion.

Clinical Vignettes/Clinical Pearls

- Infantile idiopathic scoliosis is defined as scoliosis presenting from birth until the age of 3 without a congenital, syndromic, or neuromuscular cause.
- History and physical should focus on looking for non-idiopathic causes for scoliosis.
- Standing X-rays should be obtained if possible. Supine X-rays underestimate the Cobb angle.
- Most children with infantile idiopathic scoliosis present with curves under 20°, which spontaneously resolves with growth.
- Curves with Cobb angles over 20°, apical vertebrae that overlap their associated ribs, or RVAD greater than 20° are at high risk for curve progression.
- Non-operative treatment consists of bracing or casting. Casting has been shown to reverse the curve, effectively treating scoliosis. Bracing typically is only successful at preventing curve progression.
- Surgery is reserved for failure of non-operative treatment. If the patient is near skeletal maturity, a definitive fusion may be performed. If the patient is young, growth preserving techniques must be utilized until definitive surgery can be performed.

References

1. Scoliosis Research Society: Scoliosis. https://www.srs.org/patients-and-families/conditions-and-treatments/parents/scoliosis. Accessed 11 Oct 2018.
2. Vitale MG. Development and initial validation a novel classification system for early-onset scoliosis: classification of Early-Onset Scoliosis (C-EOS). J Bone Surg Am. 2014;96:1359–67.
3. James JI. Idiopathic scoliosis; the prognosis, diagnosis, and operative indications related to curve patterns and the age at onset. J Bone Joint Surg Br. 1954;36-B:36–49.
4. Thorsness RJ, Faust JR, Behrend CJ, Sanders JO. Non-Surgical Management of Early Onset Scoliosis. J Am Acad Orthop Surg. 2015;23:519–28.
5. Murray DW, Bulstrode CJ. The development of adolescent idiopathic scoliosis. Eur Spine J. 1996;5(4):251–7.
6. Dimeglio A. Growth of the spine before age 5 years. J Pediatr Orthop B. 1993;1:102–7.
7. Gillingham BL, Fan RA, Akbarnia BA. Early onset idiopathic scoliosis. J Am Acad Orthop Surg. 2006;14:101–12.
8. Emery JL, Mithal A. The number of alveoli in the terminal respiratory unit of man during late intrauterine life and childhood. Arch Dis Child. 1960;35:544–7.
9. Dunnill MS. Postnatal growth of the lung. Thorax. 1962;17:329–33.
10. Conner AN. Developmental anomalies and prognosis in infantile idiopathic scoliosis. J Bone Joint Surg Br. 1969;51:711–3.
11. Wynne-Davies R. Infantile idiopathic scoliosis: causative factors, particularly in the first six months of life. J Bone Joint Surg Br. 1975;57:138–41.
12. Mehta MH. The rib-vertebra angle in the early diagnosis between resolving and progressive infantile scoliosis. J Bone Joint Surg Br. 1972;54(2):230–43.
13. Pahys JM, Samdani AF, Betz RR. Intraspinal anomalies in infantile idiopathic scoliosis: prevalence and role of magnetic resonance imaging. Spine (Phila Pa 1976). 2009;34(12):E434–8.

14. Tis JE, Karlin LI, Akbarnia BA, et al. Early onset scoliosis: modern treatment and results. J Pediatr Orthop. 2012;32:647–57.
15. Weinstein SL, Dolan LA, Wright JG, Dobbs MB. Effects of bracing in adolescents with idiopathic scoliosis. N Engl J Med. 2013;369:1512–21.
16. Sanders JO, D'Astous J, Fitzgerald M, et al. Derotational casting for progressive infantile scoliosis. J Pediatr Orthop. 2009;29:581–7.
17. Mehta MH. Growth as a corrective force in the early treatment of progressive infantile scoliosis. J Bone Joint Surg Br. 2005;87:1237–47.
18. Hardesty CK, Huang RP, El-Hawary R, et al. Growing Spine Committee of the Scoliosis Research Society. Early-onset scoliosis: updated treatment techniques and results. Spine Deformity. 2018;6:467–72.

Chapter 16
Congenital Muscular Torticollis

Ayesha Maqsood

The goal of this chapter is to outline a developmental abnormality observed in the pediatric cervical spine: congenital muscular torticollis.

Brief Overview of Condition

Congenital muscular torticollis (CMT), also known as congenital wryneck, is a neck deformity caused by a unilateral shortening or stiffening of the sternocleidomastoid muscle (SCM). Torticollis indicating a twisted neck causes the infant's head to tilt towards the ipsilateral side and the chin to rotate towards the contralateral side [1]. The infant usually presents with characteristic features of the deformity within its first 6–8 weeks of life [2]. The etiology of CMT remains unknown, but one of the main theories suggests that it is acquired and is due to fibrosis and subsequent contracture of the SCM muscle as a result of a stretch or injury within the muscle that is caused by abnormal positioning in utero or delivery. The treatment for CMT starts with a conservative, nonoperative approach, beginning with PT, caregiver education, and manual stretching exercises. In most cases, normal range of motion of the neck will be achieved by 1 year of age. If the CMT is persistent and does not respond to the physical therapy regimen or the patient presents after 1 year of age, SCM muscle lengthening surgery may be necessary [3].

A. Maqsood (✉)
Department of Surgery, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA
e-mail: amaqsood@luriechildrens.org

J. F. Sarwark, R. L. Carl (eds.), *Orthopaedics for the Newborn and Young Child*,
https://doi.org/10.1007/978-3-031-11136-5_16

Background Including Epidemiology and Pathophysiology

The incidence of congenital muscular torticollis by some studies has been estimated to be less than 1% of all live births; the incidence may be as low as 0.3% in uncomplicated deliveries or as high as 1.8% in breech deliveries [4]. Many clinical studies have demonstrated that infants with CMT have increased incidence of other deformations, such as developmental dysplasia of the hip (DDH) [5], with these studies recommending screening infants with CMT for DDH.

Though the etiology of CMT is unknown, there are theories that are believed to explain the deformity. These include birth trauma (stretch), in utero crowding, neurogenic myopathy, and mesenchymal precursor cells [4]. One theory suggests that trauma to the neck during birth may cause venous compression of the SCM muscle, resulting in compartment syndrome and eventually fibrosis of the muscle [4]. Another proposes that in utero crowding may cause the deformity as children who have normal, uncomplicated deliveries also exhibit CMT. Neurogenic myopathy, a combination of trauma and ischemia, leads to progressive fibrosis, which will entrap the SCM branch of the spinal accessory nerve, leading to muscle contraction and the deformity [4]. Mesenchymal precursor cells may remain in the SCM muscle after embryogenesis. These cells have the ability to differentiate into myoblasts and fibroblasts. If fibroblast differentiation dominates, excessive collagen will form, resulting in a scar-like contracture in the SCM muscle [4].

For example, Kuo et al. examined histological features of affected SCM muscle tissues in CMT patients. Their study demonstrated that the muscle had been replaced by dense fibrous tissue [5]. Upon further examination of the affected tissues with MRI, they suggested CMT may be caused by intrauterine or perinatal SCM muscle compartment syndrome [5], caused by ischemia and edema in the muscle from flexion with lateral bending and rotation of the head and neck, resulting in SCM muscle trauma [5]. The dense fibrous tissue is sometimes palpable as a fibrous mass or pseudo-tumor that presents within the first 3 weeks after birth [5]. The mass is comprised of myoblasts, fibroblasts, myofibroblasts, and mesenchymal-like cells that will mature and differentiate [5] and should not be biopsied. There is physiological justification for early physical therapy of the neck to prevent muscle fibrosis by intermittent stretching and relaxation [6].

Clinical Presentation: History and Physical

The typical clinical presentation results from a contracted SCM muscle, as seen in Fig. 16.1. In CMT, the signs and symptoms from this become apparent within the first 2 months of life. As mentioned earlier, the dense fibrous tissue of the SCM muscle tissue may form a small, firm mass (pseudo-tumor) in the middle to upper two-thirds of the SCM muscle [1]. A mass ranging from 8 mm up to 3 cm can be felt [7]. The pseudo-tumor reaches it maximum size within the first 4–6 months of life,

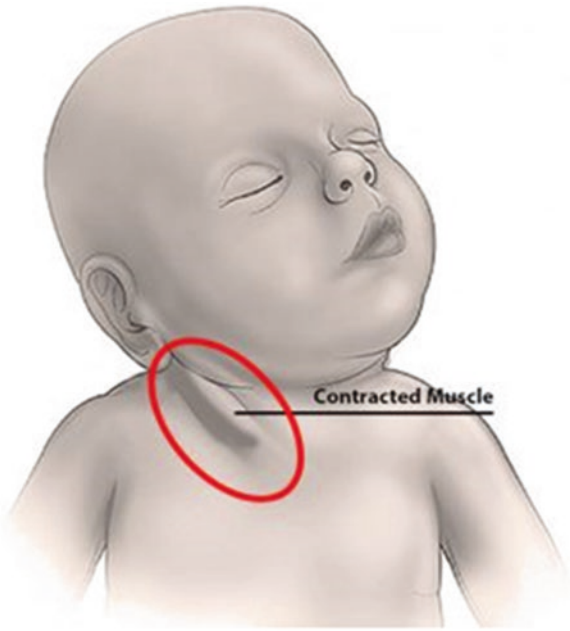


Fig. 16.1 Congenital muscular torticollis is a condition in which an infant's sternocleidomastoid muscle is contracted or shortened, causing their head to tilt towards the affected side and the chin to rotate towards the opposite side [9]. Image courtesy of Prof. Nicola Portinaro, Director of the Orthopedic Paediatric and Neuro-Orthopedic Department at Humanitas Research Hospital (Milan, Italy)—www.nicolaportinaro.com

then gradually regresses [8]. As observed in Fig. 16.1, the infant's head is also tilted to the affected side and its chin rotated to the opposite shoulder. The stiffened or shortened SCM muscle causes a limited range of neck motion, making it challenging for the infant to turn their head side to side and up and down and also causing the infant to have a strong tendency to one side, preferring to look to one side and turn their head to one side over the other. Caregivers should be aware of the infant's inclination to the side preference because it can also result in cranial asymmetry. Plagiocephaly can commonly present on the side of the contracted SCM muscle [4]. On physical examination when the head is viewed from above, the occipital flattening will be more prominent.

Children with CMT have been found to have an increased incidence of complicated deliveries [7]. At the 2-month well child check, if the physician notices a head tilt and cranial asymmetry, they should inquire about the infant's delivery. Was it complicated; did it require forceps or cesarean section, breech position or was it a twin birth [7]? They should also ask questions about the infant's sleeping, feeding, and playtime positions throughout the day. As repeatedly putting the infant in the same position can increase the cranial asymmetry.

On physical examination, the infant should be observed in their resting position in order to assess their head tilt. The physician should also gently, passively rotate and tilt the head in both direction to assess the SCM muscle's degree of stiffness and observe for a mass, if present. Typically infants will have decreased active rotation on the affected side. If cranial asymmetry is present, findings will include contralateral occipital flattening and frontal protrusion, ipsilateral zygomatic flattening and

temporal protrusion, anterior displacement of the contralateral ear, and inferior displacement of the ipsilateral ear [7]. The eye movements of the infant should also be examined, specifically looking for hypertropia. If any suspicious ocular problems arise, the infant should be referred to an ophthalmologist. Also a complete neurologic examination should be performed, to rule out nonmuscular etiologies [7]. Any positive signs should be referred to a neurologist for further examination.

Infants who are diagnosed with CMT are at an increased risk for DDH. Minihane et al. suggest that a routine physical examination is sufficient for detecting DDH in children with CMT [10]. If any abnormalities are discovered, referral should be made to an orthopedist for imaging.

Evaluation

The diagnosis of CMT is primarily clinical. A complete medical history and physical examination should be taken of the patient. A history revealing a complicated birth and a preference for one side over the other when sleeping, feeding, and playing should be a cause for concern. A physical examination revealing the characteristic head tilt, tense SCM muscle, and a palpable mass in the muscle body should be arise suspicion for CMT. In addition to the history and physical examination, diagnostic procedures can also be performed. An ultrasound can be useful in the presence of a mass. Radiographs of the cervical spine should always be obtained to ensure that the deformity is a muscular torticollis and not associated with congenital vertebral anomaly of the cervical spine [8]. Radiographs of the cervical spine in children with CMT are always normal, aside from the head tilt and rotation [8].

In addition, consideration should be given to screening patients with CMT for developmental dysplasia of the hip (DDH), as they occur concomitantly in up to 20% of infants [4]. If any suspicion exists about the status of the hips, appropriate imaging should be completed. A hip ultrasound should be obtained in children under the age of 6 months and an anteroposterior pelvic X-ray in children older than 6 months to rule out hip dysplasia if clinical examination reveals hip clicks, asymmetric hip range of motion, or asymmetric skin folds [7].

Management

When diagnosed early, CMT may be managed conservatively, rarely requiring the need for surgical intervention [11]. It was found that up to 70% of infants with CMT who were treated early, either at home or in an outpatient clinic, were able to recover normal neck movement within 12 months, with only 7% requiring surgery [12, 13]. As an infant grows, they will become more independent in their movements, making it more difficult to perform the required stretching exercises with the required frequency that is recommended. If a physician suspects CMT in a patient, they

should refer to physical therapy (PT) early. PT is considered a first-line treatment and should be prescribed to patients with CMT. An effective program consists of therapy with a trained professional along with a home program carried out by caregivers (parents). The education caregivers receiving for the infant's daily routine are essential for successful outcomes.

The goal of a physical therapy program is to stretch and restore symmetry of the neck muscles while also promoting rotation of the neck. This can be accomplished through changes made in the infant's environment, caregiver education, and manual stretching exercises. To encourage head rotation to the infant's less preferred side caregivers can implement the following techniques: placing toys on the less preferred side, alternate the side on which the infant is carried, and positioning the infant's crib in the room so that their less preferred side is facing the door. Another useful technique is placing the infant in the prone position, or tummy time, while awake. This will help strengthen the neck, shoulder, arm, and back muscles, in addition to preventing further plagiocephaly [3].

Outpatient clinics with physical therapists are highly recommended to make sure that the infant is receiving proper stretching exercises regularly, it is important to continue these exercises at home with the caregiver. Heidenreich et al. demonstrated that increased stretching frequency results in improved outcomes for infants with CMT [14]. The recommendation for effective neck-stretching exercises is to hold each stretch for 30–60 s, to do three repetitions of each stretch, and to do the series of stretches six to eight times a day [5]. Sometimes caregivers may feel reluctant to perform these manual stretching exercises at home, in fear of hurting the infant. This is why proper written and visual education should be provided to the caregiver by both the physician and physical therapist.

Microcurrent therapy may increase the efficacy of therapeutic exercise with ultrasound for the treatment of CMT involving the entire SCM muscle [15]. A randomized controlled trial compared therapeutic exercise and ultrasound with or without the addition of microcurrent. The group receiving the microcurrent demonstrated a shorter treatment duration, improved neck rotation, and decreased involved SCM muscle thickness [14].

Surgical measures for treatment of CMT may be considered when cases become refractory to other therapies, such as PT and botulinum toxin type A, or when CMT is identified after 1 year of age. The SCM muscle release procedure will lengthen the muscle. Surgical techniques to accomplish this include a unipolar release, a bipolar release, endoscopic release, and subperiosteal lengthening [5]. The bipolar release combined with a Z-plasty of the sternal attachment has yielded a 92% satisfactory result with improved cosmetic results due to the Z-plasty maintaining the V contour of the neck [8]. Endoscopic release has also been shown to have favorable long-term results [14]. Surgery today, is rare.

After surgery, PT is highly recommended to help the infant with range of motion of the neck. Children who require surgical management of their CMT tend to have more severe involvement of the SCM muscle. In these children, their prolonged experience in atypical postures may result in potentially asymmetrical development of the visual, vestibular, and proprioceptive systems [16]. Oledska et al.

demonstrated that post-surgical therapy through visual, vestibular, and proprioceptive stimuli could reestablish their midline [16].

Positional plagiocephaly is an oblique flattening of one side of the infant's head associated with prolonged and asymmetric pressure on the head [3]. It is commonly associated with CMT because the infants have a tendency to keep their head tilted towards one side. Repositioning therapy is one method to treat the plagiocephaly. This is when the infant is placed in different positions throughout the day to relieve pressure on the flattened side of the head. Though research studies have shown considerable evidence that molding therapy with an orthotic may reduce skull asymmetry more effectively than repositioning therapy [17]. A cranial orthotic, or helmet, may be used in order to restore the normal shape of the infant's head. The optimal time to use an orthosis is between 4 and 12 months of age, as the first year of life is when the skull grows the fastest and is most malleable [7]. It is recommended that it be worn 23 h a day for 3–6 months, but duration can vary depending on when the CMT resolves [7].

In children who are unresponsive to PT and whose parents want another alternative before surgical intervention, botulinum toxin type A may rarely be used. Also known as onabotulinumtoxin A, it is a neurotoxin derived from the bacteria *Clostridium botulinum*, which reduces muscle activity by inhibiting release of acetylcholine [7]. It can increase the effectiveness of stretching the SCM muscle and strengthening the overstretched and weakened muscles on the opposite side of the contracture. Retrospective studies have shown it to be safe in children with refractory CMT [18, 19].

Clinical Vignettes/Clinical Pearls

A common case of congenital muscular torticollis will present as follows:

A 3-month-old female presents with a left head tilt and skull deformity. Shortly after birth, the patient's parents observe a tendency for her to turn her head to the right. A few weeks after that they note right occipital flattening. The patient is a twin, born at 38 weeks gestation via an uncomplicated vaginal delivery. Patient sleeps supine and tends to keep her head turned to the right. Patient is meeting her milestones appropriately although she dislikes the prone position and has limited tummy time. Physical examination reveals plagiocephaly with moderate right occipital flattening, mild right frontal protrusion, mild left temporal protrusion, and mild left zygoma flattening. Patient's right ear is displaced anteriorly when viewed superiorly. Patient's passive head position in supported sitting reveals a 15° left tilt and right rotation. Patient also lacks the last 20° of active left rotation and has difficulty turning her head to the right. Patient cries when placed prone and only extends her head briefly. Ocular, hip, and neurologic exams are normal [7].

CMT can also present in an atypical fashion. Some of these incidences are highlighted here:

Atypical cases of CMT are those with a nonmuscular cause including congenital superior oblique palsy, congenital vertebral anomalies, neurologic abnormalities, and infection. Patients with congenital superior oblique palsy (ocular torticollis) tend to tilt their head away from the side of the weak superior oblique muscle in order to restore binocular vision. On physical examination if the head is passively tilted towards the affected side, hypertropia or vertical deviation of the eye may be observed but is not always obvious. Also plagiocephaly can develop. Patients with congenital vertebral segmentation anomalies, such as hemivertebrae or Klippel-Feil syndrome, present with a head tilt and can also have associated cervicothoracic scoliosis. Intermittent torticollis associated with neurologic symptoms may indicate a posterior fossa or spinal cord tumor. A transient inflammatory illness could also result in an acute onset of torticollis. Retropharyngeal abscessed and pyogenic cervical spondylitis are unusual infectious causes of torticollis. Sandifer Syndrome is an association of gasteroesophageal reflux and torticollis, but it is more of a spasmodic torsional variant [7].

Natural History, Primary and Secondary Prevention

In a prospective study, Stellwagen et al. identified 16% of newborns with evidence of congenital muscular torticollis, making it one of the most common congenital musculoskeletal abnormality [20]. The characteristic features of CMT, include the infant's head tilted towards the affected side and its chin rotated towards the unaffected side, present within the first few weeks of life. The diagnosis of CMT may be made clinically and verified with imaging. The majority of CMT cases will resolve after several months of conservative care with manual stretching and physical therapy [21]. The natural history of CMT consists of persistence torticollis, facial asymmetry, and plagiocephaly [22]. If after conservative care there are still residual range of motion deficits or a late presentation of CMT, surgical lengthening of the SCM may be required for correction.

The primary prevention of CMT entails proper caregiver education by an experienced pediatrician and physical therapist. The education should not only include a proper understanding of the condition but also the treatment and how the caregiver can be involved in the process to the infant's recovery. If diagnosed early enough, most cases of CMT are successfully treated conservatively with neck stretching exercises [5]. For this reason, it is essential for the caregiver to be actively engaged and feel comfortable performing the stretching exercises on the infant. Caregivers may be hesitant to perform the stretching exercises effectively because they feel they are causing pain to the infant and may even injure them. Therefore, it is not only crucial for the pediatrician and physical therapist to verbally explain the stretching exercises but also visually demonstrate them on the infant. It would also prove useful to provide reassurance to the caregiver that if done properly, the exercises they are performing are not harming the infant but aiding in their recovery.

When treating infants, the goal should be to spare the child from expensive or invasive interventions, such as cranial orthotics or surgery [5]. Secondary prevention should include early screening for CMT, 1–2 days after birth. In order to have the most successful treatment outcome, early PT intervention is critical. Upon discovering any asymmetries in the head or neck posture, infants should be referred to a physical therapist immediately. The physical therapist should perform a comprehensive systems review, giving special attention to screening the infant's vision, gastrointestinal functions, positional preference, and structural and movement asymmetries of the head, neck, spine, trunk, hips, and upper and lower extremities [23]. If after 4–6 weeks of therapy there is little to no improvement in the infant's condition, the physical therapist should make a referral back to the physician for further work-up and possible recommendation of surgery.

References

1. Ann & Robert H. Lurie Children's Hospital of Chicago. Congenital muscular torticollis & causes. 2018. https://www.luriechildrens.org/en/specialties-conditions/congenital-muscular-torticollis/. Accessed 30 Oct 2018.
2. OrthoInfo. Congenital Muscular Torticollis (Twisted Neck). 2018. https://orthoinfo.aaos.org/en/diseases%2D%2Dconditions/congenital-muscular-torticollis-twisted-neck/. Accessed Oct 30 2018.
3. Doyle SM. Congenital muscular torticollis: an overview. Hospital for Special Surgery. 2018. https://www.hss.edu/conditions_congenital-muscular-torticollis.asp. Accessed Oct 30 2018.
4. POSNA. Pediatric Orthopaedic Society of North America. Congenital muscular torticollis. 2018. https://posna.org/Physician-Education/Study-Guide/Congenital-Muscular-Torticollis. Accessed 30 Oct 2018.
5. Kuo AA, Tritasavit S, Graham JM Jr. Congenital muscular torticollis and positional plagiocephaly. Pediatr Rev. 2014;35(2):79–87.
6. Graham JM Jr. Congenital muscular torticollis. In: Recognizable patterns in human deformation. 3rd ed. Philadelphia, PA: Elsevier; 2007. p. 130–40.
7. Epocrates. An Athena Health Service. Congenital muscular torticollis. 2018. https://online.epocrates.com/diseases/75922/Congenital-torticollis/Common-Vignette. Accessed Oct 30 2018.
8. Loder RT, Hensinger RN. Developmental abnormalities of the cervical spine. In: Weinstein SL, editor. The pediatric spine principles and practice. New York, NY: Raven Press Ltd; 1994. p. 397–400.
9. Nicola Portinaro, Director of the Orthopedic Paediatric and Neuro-Orthopedic Department at Humanitas Research Hospital. Milan, Italy. www.nicolaportinaro.com.
10. Minihane KP, Grayhack JJ, Simmons TD, Seshadri R, Wysocki RW, Sarwark JF. Developmental dysplasia of the hip in infants with congenital muscular torticollis. Am J Orthop. 2008;37(9):155–8.
11. Nilesh K, Mukherji S. Congenital muscular torticollis. Ann Maxillofac Surg. 2013;3(2):198–200.
12. Carenzio G, Carlisi E, Morani I, Tinelli C, Barak M, Bejor M, et al. Early rehabilitation treatment in newborns with congenital muscular torticollis. Eur J Phys Rehabil Med. 2015;51(5):539–45.
13. Binder H, Eng GD, Gaiser JF, Koch B. Congenital muscular torticollis: results of conservative management with long-term follow-up in 85 cases. Arch Phys Med Rehabil. 1987;68:222–5.

14. Heidenreich E, Johnson R, Sargent B. Informing the update to the physical management of congenital muscular torticollis evidence-based clinical practice guidelines. Pediatr Phys Ther. 2018;30(3):164–75.
15. Kwon DR, Park GY. Efficacy of microcurrent therapy in infants with congenital muscular torticollis involving the entire sternocleidomastoid muscle: a randomized placebo-controlled trial. Clin Rehabil. 2014;28(10):983–91.
16. Oledzka M, Suhr M. Postsurgical physical therapy management of congenital muscular torticollis. Pediatr Phys Ther. 2017;29(2):159–65.
17. Xia JJ, Kennedy KA, Teichgraeber JF, Wu KQ, Baumgartner JB, Gateno J. Nonsurgical treatment of deformational plagiocephaly: a systematic review. Arch Pediatr Adolesc Med. 2008;162:179–727.
18. Oleszek JL, Chang N, Apkon SD, Wilson PE. Botulinum toxin type a in the treatment of children with congenital muscular torticollis. Am J Phys Med Rehabil. 2005;84(10):813–6.
19. Joyce MB, de Chalain TM. Treatment of recalcitrant idiopathic muscular torticollis in infants with botulinum toxin type A. J Craniofac Surg. 2005;16:312–27.
20. Stellwagen L, Hubbard E, Chambers C, Jones KL. Torticollis, facial asymmetry and plagiocephaly in normal newborns. Arch Dis Child. 2008;93(10):827–31.
21. Frizzell K, Malik A, Herman MJ, Pizzutillo P. Congenital muscular torticollis. In: Phillips J, Hedequist D, Shah S, Yaszay B, editors. The management of disorders of the child's cervical spine. Boston: Springer; 2018. p. 183–90.
22. Sarwark JF, editor. Essentials of musculoskeletal care 4. 4th ed. Chicago, IL: American Academy of Orthopaedic Surgeons; 2010. p. 1194–8.
23. Suhr MC, Oledzka M. Considerations and intervention in congenital muscular torticollis. Curr Opin Pediatr. 2015;27:75–81.

Chapter 17
Arthrogryposis: Overview and Evaluation

Ognjen Stevanovic

Overview

Arthrogryposis has been used to describe physical manifestations of multiple joint contractures in numerous, unrelated diseases. As the name implies, these patients suffer from joint contractures (arthron—joint, grūpōsis—hooking). Confusion has been made over the years with regard to this term and it has been used interchangeably to describe conditions that are otherwise unrelated but share same phenotypic manifestations. Rosenkranz in 1905 [1] was the first to use the term arthrogryposis while Stern [2] in 1923 described three patients what is now considered the classical and most common manifestation of arthrogryposis, involving symmetrical joint stiffness, internal rotation of the shoulders, naming it arthrogryposis multiplex congenita. This constellation of symptoms in the most common form has also been termed amyoplasia, due to the fact that most of these deformities were thought to be due to the underdevelopment of muscle introduced by Sheldon in 1932 [3]. Nowadays, term arthrogryposis indicates a clinical picture that is part of a syndrome which manifests as multiple joint contractures present at birth.

Classification

Currently, there are more than 300 syndromes that present with joint contractures consistent with features of arthrogryposis [4–7]. This makes a definitive diagnosis very challenging. Hall developed a differentiation system of arthrogryposis in order to facilitate development of a differential diagnosis [7]. This entailed three broad groups, of which the first one consisted of patients having mainly limb involvement.

O. Stevanovic (✉)
Department of Orthopaedic Surgery, Northwestern University, Chicago, IL, USA

J. F. Sarwark, R. L. Carl (eds.), *Orthopaedics for the Newborn and Young Child*,
https://doi.org/10.1007/978-3-031-11136-5_17

This includes “classic arthrogryposis” or amyoplasia, as well as several camptodactyly syndromes and distal arthrogryposis type 1, among others. Group 2 involved disorders with limb involvement along with other body parts but excluding central nervous system. Finally, group 3 consists of patients with limb involvement and central nervous system dysfunction. Arriving at a diagnosis is challenging task, and a clinician must thoroughly and carefully evaluate the patient and all aspects of the medical history. Collaboration with an experienced geneticist is often required, especially with the rarer diseases which manifest arthrogryposis features.

Epidemiology

Arthrogryposis is a very rare finding, occurring in 1 out of every 3000–5000 live births [8–10], but recent epidemiologic study by Hoff et al. describes the prevalence in European countries to be as low as 8.5 per 100,000 [11]. This accentuates the extraordinary rarity of the specific diseases that the arthrogryposis is the manifestation of.

Pathophysiology

Fetal akinesia is the primary driving force towards the development of arthrogryposis. In the early stages of development, embryologically, the joints are unaffected. Nevertheless, once factors inducing hypomobility are introduced, this development changes course to produce aberrant features and at that point it becomes a self-propagating cycle. Decreased movement increases fibrotic tissue proliferation surrounding the joints, which further impairs any effort to mobilize as the compliance of the joint capsule is decreased as well as the ability of the muscles and tendons to stretch [12]. This relative immobility leads to muscle atrophy from disuse as well as reshaping and dysplasia of joint surface due to uneven loading and joint reactive forces [13].

This hypothesis has been tested on animal models where immobility has been induced by different means, targeting biochemical pathways. Exposure to Coxsackie virus, Newcastle viruses or antagonism of nicotinic acetylcholine receptors with curare produced ankylosis and joint stiffness in chickens, resembling arthrogryposis [14, 15]. Moessinger et al. reported a constellation of symptoms including multiple joint contractures, pulmonary hypoplasia, short umbilical cord, hypoplasia of the jaw, and polyhydramnios when the latter agent was administered to rats [16]. This is called fetal akinesia sequence deformation. Similar presentation in humans, described by Pena and Shokeir [17, 18], is the most severe form of arthrogryposis with a poor prognosis.

The longer duration and earlier onset of hypokinesia are directly proportional to severity of contractures. Fetus starts to move spontaneously at about eighth week of

gestation, and this is vital for joint development. It is thought that any immobilization beyond 3 weeks may lead to pathologic manifestations.

Etiology

Determining the etiology of akinesia has been a challenge, nevertheless, extensive research has been done on this topic and major discoveries have been made. As a clinical manifestation of more than 300 diseases, needless to say, the etiology is multifactorial. Hall [7] groups these etiologies into ten broad categories (see Table 17.1).

Each of these lead towards common pathway, which is fetal joint immobility, ultimately resulting in contractures. Pathologies involving any part of the neuromuscular apparatus will predictably manifest clinical features of arthrogryposis. This can involve structural or functional defects of myocytes, their interface with the axonal endings at the neuromuscular junction or ion transport. Conditions based on muscular pathology known to induce symptoms of arthrogryposis include congenital muscular dystrophies, congenital myopathies, intrauterine myositis, and mitochondrial disorders. Similarly, any aspect of the nerve developed aberrantly will cause downstream effects, affecting the muscles, precluding normal intrauterine movement and facilitate formation of contractions. Notable defects include anomalous development of anterior horn cells [19–22], myelination [23, 24], neural tube defects, or abnormalities in signal conduction at the neural cleft [25, 26]. These defects can be in central or peripheral nervous system. Conditions presenting a physical barrier to movement are also important to recognize, including periarticular and connective tissue disease (i.e., trismus pseudocamptodactyly, Larsen's syndrome, multiple pterygium syndrome, congenital arachnodactyly, osteogenesis imperfecta, etc.). Finally, maternal factors play a crucial role and can range from

Table 17.1 Etiology categories

1.	Myopathic processes
2.	Neuropathic processes
3.	Neuromuscular end-plate abnormalities
4.	Connective tissue abnormalities
5.	Space limitations
6.	Maternal illness
7.	Maternal exposures
8.	Blood supply compromise to placenta and/or fetus
9.	Metabolic disturbances
10.	Epigenetic disorders

gross anatomic barriers such as uterine dysplasia (bicornate uterus), multiparity, fibroids, oligohydramnios, tumors [7] to systemic factors involving maternal illnesses and the role of environmental factor during gestational period. These are well recognized and include diabetes mellitus, multiple sclerosis [27], myasthenia gravis [28, 29], viral exposers (rubeola rubella, Coxsackie encephalitis) [30].

Genetics

Roles of numerous genes have been identified that are associated with arthrogryposis. Primary role of these genetic alterations is induction of a specific syndrome or disease, which in turn have clinical features of arthrogryposis. Hence, the spectrum of genetic etiologic factors is full, ranging from single gene disorders, chromosomal abnormalities, deletion, translocations, duplications, mitochondrial disorders. Not surprisingly, many of these mutations may manifest similar or nearly identical clinical features [31].

Clinical Presentation

Patients typically do not have cognitive developmental delay. Classic arthrogryposis (amyoplasia) is characterized by symmetric involvement of upper and lower extremities. Axial skeleton is not frequently involved, and it is not uncommon that these patients have unaffected neck and head movement. Nevertheless, there may be involvement of the spine, and these patients can present with progressing neuromuscular scoliosis [32–34].

Patients are born with upper extremities in characteristic position of shoulder adduction and internal rotation, elbow extension, volar wrist flexion, and ulnar deviation of the hands (Fig. 17.1). While deltoid function is often diminished, there may be some flexion allowed. Elbow joint is quite stiff secondary to atrophy of brachialis and biceps brachii, allowing for minimal passive flexions. Joint creases are commonly absent due to immobility in utero. There is also diffuse muscle atrophy and replacement of the myocytes by adipose tissue, and the limbs tend to adopt a "sausage-resembling" appearance. The fingers are quite stiff, and there is minimal motion of the thumbs as they are usually in adducted position.

Lower extremities are also similar in presentation. Hips often have some preservation of range of motion, however in patients with advanced contractures are predisposed to hip subluxation and eventually, dislocations [32]. Knees may be stuck in flexion or extension. Foot and ankle deformities are almost universally present and often involve equinovarus deformities. Of note, patients also may present with midfacial hemangioma and micrognathia, gastroschisis, bowel atresia, inguinal hernia, and other abnormalities. Similarly, as in upper extremities, muscle mass is diminished and in often replaced by adipose tissue secondary to disuse.

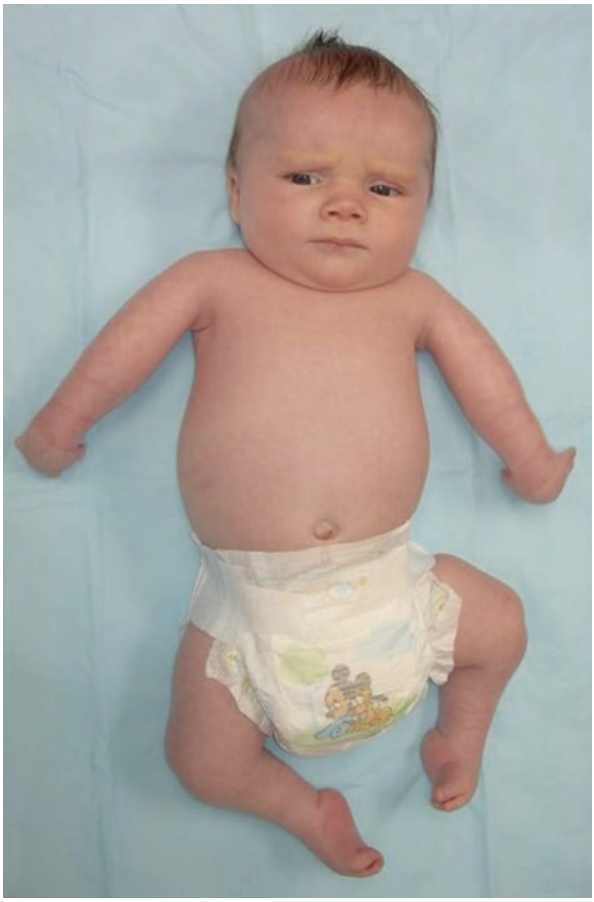


Fig. 17.1 Infant with arthrogryposis, displaying features including internal rotation of the shoulder, elbow extension, wrist flexion, as well as flexion contracture of the knee and equinovarus deformity of bilateral feet. Reprinted with permission from Bamshad M, Van Heest AE, Pleasure D. Arthrogryposis: a review and update, Journal of Bone and Joint Surgery, Vol.91/Suppl 4, pgs 40–46, © 2009. https://journals.lww.com/jbjsjournal/Citation/2009/07004/Arthrogryposis__A_Review_and_Update.6.aspx [35]

Distal arthrogryposis is a collection of syndromes which mainly involve the most distal aspects of the limbs and some have a strong genetic basis with predictable inheritance patterns, mainly being autosomal dominant. There have been at least ten types of distal arthrogryposes types described and assigned sequential names (i.e., DA1, DA2, etc.). This categorization is based on the number of overlapping features between presentations. Diagnosis of DA is clearly defined and must include at least 2 hallmark features unless there is a family history in the first degree relative, in which case only 1 criterion must be met. For the upper extremity, these include camptodactyly or pseudocamptodactyly, hypoplastic or absent flexion creases of the fingers, overriding fingers, and ulnar deviation of the wrist. With regard to lower extremity, criteria include presence of talipes equinovarus, congenial vertical talus, flat foot, pes calcaneovalgus, and metatarsus adductus [35].

Evaluation

Accurate diagnosis of arthrogryposis and its underlying syndrome is major clinical challenge and requires specialty evaluation (genetics or neurology) that should ideally start in the prenatal period. This process should involve a thorough pregnancy history, maternal illnesses, preexisting conditions, fetal complications (i.e., oligo/polyhydramnios, fetal movement), and drug or environmental exposures. Any problems with delivery should be noted, such as length of gestation, intrauterine anatomic variants or masses (i.e., fibroids). A thorough, 3-generation family history is essential, considering that many of the arthrogryposis syndromes have a strong genetic and molecular basis. Finally, physical exam of the child is of utmost importance. Joints and severity of involvement, aspect of the limb (proximal vs distal), and resting position should be methodically documented and followed over time. Other abnormalities can be easily missed due to obvious contracture malformations. These include urogenital malformations (cryptorchidism, lack of labia, microphallus), defects of the jaw, face (asymmetry, flat bridge of nose), skin (hemangiomas, dimples, hirsutism), abdominal wall defects (gastroschisis, hernias), and others.

Via routine prenatal ultrasounds, fetal mobility may be assessed as early as 8 weeks gestation. Nevertheless, most of the abnormalities are discovered later on, typically in second or third trimester. This can prepare clinician to be vigilant and weary of the prospect of the child being delivered with contracture abnormalities and may alter delivery planning. Ideally, any traumatic exposure to the weakened limbs of the child should be minimized. C-section would be a reasonable option to offer mothers in whom their fetuses may be in the early stages in developing arthrogryposis. Majority of patients are not diagnosed in the newborn period, but rather their further development, pattern of joint involvement, severity of disease, response to treatment narrow the diagnosis.

Imaging and laboratory evaluation will be guided by the clinical exam and history, which would often include X-rays, MRI of the spine and brain, and genetic studies.

Treatment

Treatment of a patient with arthrogryposis is mainly focused on improving their quality of life and enhancing functionality. These are often intelligent individuals, and a focus must be maintained to provide the treatment without compromising their normal cognitive and intellectual development. Goals of treatment include complete independence with activities of daily living, permitting unaffected social interaction, enhancing mobility by improving contractures in order to enable standing and walking, and preservation of mobility of joints that are less affected. To achieve these goals, we often must resort to surgical intervention. These are done in conjunction with extensive therapy, stretching, and orthoses. It should be

emphasized that deformities in arthrogryposis are not always responsive this treatment modality as the joints are not simply stiff because of contracture or fibrosis of a single component. These joints have been immobile since in utero so multiple parts of the joint are dysplastic, including the joint line congruency, capsule, muscles crossing the joint, and tendon insertions. Therefore, simple releases are often ineffective, and a strategic approach must be used in order to identify which structures are in the way of restoring or improving the range of motion. At the same time, most of the surgical interventions are preferably done early in the childhood as the response of the patients to rehabilitation protocol and further development is most adaptable in this period.

Treatment of a patient with arthrogryposis is an arduous and long rehabilitation process that should involve multiple specialists, including a surgeon, physical therapist, and a pediatrician. Importantly, it should be tailored to individual patient's needs, and, critically, involve the patient and their family who should be driving the whole process. Focus can often be lost on achieving one of the goals mentioned above (commonly ambulation or standing) and neglecting other areas of improvement (upper extremity functionality), as opposed to simultaneously tackling all areas that can be treated.

References

1. Rosencrantz E. Ueber kongenitale kontracturen der oberen extremitaten. Z Orthop Chir. 1905;14:52.
2. Stern WG. Arthrogryposis multiplex congenita. JAMA. 1923;81(18):1507–10.
3. Sheldon W. Amyoplasia congenita. Arch Dis Child. 1932;7:117–36.
4. Hall JG, Reed SD, Greene G. The distal arthrogryposes: delineation of new entities—review and nosologic discussion. Am J Med Genet. 1982;11(2):185–239.
5. Medicine JHUSo. Online Mendelian inheritance in man. https://www.ncbi.nlm.nih.gov/omim. Accessed Oct 2018.
6. Bamshad M, Jorde LB, Carey JC. A revised and extended classification of the distal arthrogryposes. Am J Med Genet. 1996;65(4):277–81.
7. Hall JG. Arthrogryposis (multiple congenital contractures): diagnostic approach to etiology, classification, genetics, and general principles. Eur J Med Genet. 2014;57(8):464–72.
8. Lowry RB, Sibbald B, Bedard T, Hall JG. Prevalence of multiple congenital contractures including arthrogryposis multiplex congenita in Alberta, Canada, and a strategy for classification and coding. Birth Defects Res A Clin Mol Teratol. 2010;88(12):1057–61.
9. Hall JG, Vincent A. Arthrogryposis. In: Jones HR, DeVivo DC, Darras BT, editors. Neuromuscular disorders of infancy, childhood and adolescence A clinician's approach. Philadelphia, PA: Butterworth Heinemann; 2003. p. 123–41.
10. Darin N, Kimber E, Kroksmark AK, Tulinius M. Multiple congenital contractures: birth prevalence, etiology, and outcome. J Pediatr. 2002;140(1):61–7.
11. Hoff JM, Loane M, Gilhus NE, Rasmussen S, Daltveit AK. Arthrogryposis multiplexa congenita: an epidemiologic study of nearly 9 million births in 24 EUROCAT registers. Eur J Obstet Gynecol Reprod Biol. 2011;159(2):347–50.
12. Swinyard CA. Concepts of multiple congenital contractures (arthrogryposis) in man and animals. Teratology. 1982;25(2):247–58.

13. Simonian PT, Staheli LT. Periarticular fractures after manipulation for knee contractures in children. J Pediatr Orthop. 1995;15(3):288–91.
14. Drachman DB, Coulombre AJ. Experimental clubfoot and arthrogryposis multiplex congenita. Lancet (London, England). 1962;2(7255):523–6.
15. Robertson GG, Williamson AP, Blattner RJ. A study of abnormalities in early chick embryos inoculated with New Castle disease virus. J Exp Zool. 1955;129:5–43.
16. Moessinger AC. Fetal akinesia deformation sequence: an animal model. Pediatrics. 1983;72(6):857–63.
17. Pena SD, Shokeir MH. Syndrome of camptodactyly, multiple ankyloses, facial anomalies, and pulmonary hypoplasia: a lethal condition. J Pediatr. 1974;85(3):373–5.
18. Shenker L, Reed K, Anderson C, Hauck L, Spark R. Syndrome of camptodactyly, ankyloses, facial anomalies, and pulmonary hypoplasia (Pena-Shokeir syndrome): obstetric and ultrasound aspects. Am J Obstetr Gynecol. 1985;152(3):303–7.
19. Vuopala K, Leisti J, Herva R. Lethal arthrogryposis in Finland—a clinico-pathological study of 83 cases during thirteen years. Neuropediatrics. 1994;25(6):308–15.
20. Fedrizzi E, Botteon G, Inverno M, Ciceri E, D'Incerti L, Dworzak F. Neurogenic arthrogryposis multiplex congenita: clinical and MRI findings. Pediatr Neurol. 1993;9(5):343–8.
21. Bingham PM, Shen N, Rennert H, Rorke LB, Black AW, Marin-Padilla MM, et al. Arthrogryposis due to infantile neuronal degeneration associated with deletion of the SMNT gene. Neurology. 1997;49(3):848–51.
22. Burglen L, Amiel J, Viollet L, Lefebvre S, Burlet P, Clermont O, et al. Survival motor neuron gene deletion in the arthrogryposis multiplex congenita-spinal muscular atrophy association. J Clin Invest. 1996;98(5):1130–2.
23. Boylan KB, Ferriero DM, Greco CM, Sheldon RA, Dew M. Congenital hypomyelination neuropathy with arthrogryposis multiplex congenita. Ann Neurol. 1992;31(3):337–40.
24. Charnas L, Trapp B, Griffin J. Congenital absence of peripheral myelin: abnormal Schwann cell development causes lethal arthrogryposis multiplex congenita. Neurology. 1988;38(6):966–74.
25. Hoffmann K, Muller JS, Stricker S, Megarbane A, Rajab A, Lindner TH, et al. Escobar syndrome is a prenatal myasthenia caused by disruption of the acetylcholine receptor fetal gamma subunit. Am J Hum Genet. 2006;79(2):303–12.
26. Morgan NV, Brueton LA, Cox P, Greally MT, Tolmie J, Pasha S, et al. Mutations in the embryonal subunit of the acetylcholine receptor (CHRNG) cause lethal and Escobar variants of multiple pterygium syndrome. Am J Hum Genet. 2006;79(2):390–5.
27. Livingstone IR, Sack GH Jr. Arthrogryposis multiplex congenita occurring with maternal multiple sclerosis. Arch Neurol. 1984;41(11):1216–7.
28. Riemersma S, Vincent A, Beeson D, Newland C, Hawke S, Vernet-der Garabedian B, et al. Association of arthrogryposis multiplex congenita with maternal antibodies inhibiting fetal acetylcholine receptor function. J Clin Invest. 1996;98(10):2358–63.
29. Vincent A, Jacobson L, Plested P, Polizzi A, Tang T, Riemersma S, et al. Antibodies affecting ion channel function in acquired neuromyotonia, in seropositive and seronegative myasthenia gravis, and in antibody-mediated arthrogryposis multiplex congenita. Ann N Y Acad Sci. 1998;841:482–96.
30. Dalton P, Clover L, Wallerstein R, Stewart H, Genzel-Boroviczeny O, Dean A, et al. Fetal arthrogryposis and maternal serum antibodies. Neuromuscul Disord. 2006;16(8):481–91.
31. Narkis G, Landau D, Manor E, Ofir R, Birk OS. Genetics of arthrogryposis: linkage analysis approach. Clin Orthop Relat Res. 2007;456:30–5.
32. Sarwark JF, MacEwen GD, Scott CI Jr. Amyoplasia (a common form of arthrogryposis). J Bone Joint Surg Am. 1990;72(3):465–9.
33. Herron LD, Westin GW, Dawson EG. Scoliosis in arthrogryposis multiplex congenita. J Bone Joint Surg Am. 1978;60(3):293–9.
34. Daher YH, Lonstein JE, Winter RB, Moe JH. Spinal deformities in patients with arthrogryposis. a review of 16 patients. Spine. 1985;10(7):609–13.
35. Bamshad M, Van Heest AE, Pleasure D. Arthrogryposis: a review and update. J Bone Joint Surg Am. 2009;91(Suppl 4):40–6.

Chapter 18
Distal Arthrogryposis and Arthrogryposis Syndromes with Diffuse Involvement (Amyoplasia)

Kristine Santos Martin and Diane Dudas Sheehan

Brief Overview of Condition

Arthrogryposis is a congenital, non-progressive disorder that is not a single pathology, but rather a collection of conditions of varying etiologies that are characterized by joint stiffness and contractures affecting at least two different areas of the body [1]. Arthrogryposis is associated with muscle wasting and fusiform joint configuration [2]. Distal arthrogryposis includes bilateral pes equinovarus (BPEV). Arthrogryposis multiplex congenita (AMC) comprises conditions characterized by multiple joint contractures at birth and dislocations [3, 4].

Amyoplasia is the most common recognizable form of arthrogryposis characterized by symmetric limb involvement, some truncal sparing, normal to above average intelligence, and often a characteristic midline facial hemangioma [4].

The term "arthrogryposis" is derived from the Greek words for joint (arthros) and hooked (gryphon). The classic term amyoplasia (a = no, myo = muscle, plasia = development) or poor fetal muscle development was considered the primary basis for the condition; however, there are many other potential causes. Akinesia, the loss or impairment of the power of voluntary movement is associated with the condition [1].

K. S. Martin (✉)
Division of Orthopaedic Surgery and Sports Medicine, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA
e-mail: KSantosMartin@luriechildrens.org

D. D. Sheehan
Division of Orthopaedic Surgery and Sports Medicine, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA

Department of Physical Medicine and Rehabilitation, Northwestern University Feinberg School of Medicine, Chicago, IL, USA
e-mail: DSheehan@luriechildrens.org

J. F. Sarwark, R. L. Carl (eds.), *Orthopaedics for the Newborn and Young Child*,
https://doi.org/10.1007/978-3-031-11136-5_18

Arthrogryposis can occur alone or be associated with multiple developmental defects and be a part of a large number of syndromes with or without central nervous system (CNS) involvement [3]. It includes more than 400 described conditions or specific disorders linked to over 350 genes [4].

Of children with AMC, 1/3 have predominantly limb involvement (e.g., amyoplasia, distal arthrogryposis), 1/3 have limb and other body areas involved (e.g., pterygium syndrome, Larson syndrome, skeletal dysplasia), and 1/3 have limb and central nervous system involvement (e.g., myelomeningocele) [4].

Background Including Epidemiology and Pathophysiology

Joint development occurs during embryogenesis in the first 8 weeks of intrauterine life. Movement must occur for joints to remain healthy and to continue to develop normally. Restriction of intrauterine movement leads to contractures, and the severity of the contractures correlates with the time of onset of akinesia and duration in utero [1]. Decreased fetal movements, whether from central nervous system abnormalities or restrictive dermopathy, are the foundation of multiple contractures and other sequence anomalies [5].

Causes for Decreased Fetal Movement Include

1. Fetal neuropathic abnormalities, the most common cause of arthrogryposis, include dysgenesis of anterior horn cells of the spinal cord or motor nuclei in the brainstem, neural tube defects (e.g., meningomyelocele, anencephaly), sacral agenesis, spinal muscular atrophy, and myelodysplasia.
2. Fetal muscle abnormalities, a relatively rare cause, include congenital muscular dystrophies, congenital myopathies, intrauterine myositis, mitochondrial disorders.
3. Fetal connective tissue abnormalities in tendon, bone, or joint lining (e.g., synostosis, diastrophic dysplasia, metatropic dwarfism), laxity of joints with dislocations (e.g., Larson syndrome), and soft tissue fixations (e.g., pterygium syndrome).
4. Fetal intrauterine immobility due to reduced uterine space or uterine structural abnormalities (e.g., oligohydramnios, multiple fetuses, fibroids, early persistent leakage of amniotic fluid).
5. Intrauterine vascular compromise (e.g., severe maternal bleeding, failed attempts at termination of pregnancy).

6. Maternal disorders (e.g., multiple sclerosis, diabetes mellitus, myotonic dystrophy); autoimmune myasthenia gravis (due to the transfer of nicotinic acetylcholine, receptor (nAChR) antibodies via the placenta into the fetal blood stream); infections (e.g., rubella, poliomyelitis); drugs/chemicals (phenytoin, alcohol, and curare); trauma; vitamin deficiency; hyperthermia (e.g., prolonged sauna); radiation [2, 3, 6].

Incidence

Arthrogryposis incidence estimated 1 in 3000 live births with equal gender distribution [2, 4, 6].

Early Identification

Prenatal detection with screening policies can increase identification of these disorders as early as the first trimester. Increased clinician awareness and training, improved accuracy of diagnostic testing: amniocentesis, chorion sampling, ultrasonography screening, including sequential tests or advanced ultrasound examination (AUE), and other techniques such as inclusion of motor assessment support timely prenatal diagnosis.

Screening ultrasounds (US) can identify the following: contractures in the upper and/or lower limbs (multiple contractures), reduced motility, facial anomalies (flattening of facial profile and reduced prominence of the lips), and repeating US with increasing gestational age, may identify growth restriction, reduced cardiothoracic ratio, and polyhydramnios.

Prenatal diagnosis may include advanced ultrasonography (AUE) through increased duration of US testing with differentiation into specific movement patterns (general movements and isolated movements in the arms, legs, head, and spine) and calculation of reduced frequency, diminished quality, and decreased variation of these general movements help to diagnosis abnormalities comparing from a normal population examined throughout gestation 8–40 weeks [2, 7].

Differential diagnosis includes bilateral brachial plexus palsy, bony fusion (symphalangism of the phalanges), carpal or tarsal coalition, humeroradial or radioulnar synostosis, absence of dermal ridges, absence of distal interphalangeal (DIP) joint creases, amniotic bands, antecubital webbing, camptodactyly, congenital clasped thumbs, familial impaired pronation and supination of the forearm, Liebenberg syndrome, nail-patella syndrome, Nievergelt-Pearlman syndrome, Poland anomaly, Tel-Hashomer camptodactyly, trismus pseudocamptodactyly [6, 8].

Clinical Presentation: History and Physical

Amyoplasia or Classical Arthrogryposis

Amyoplasia present in the newborn period is non-genetic, sporadic, and does not increase the risk of having another affected child [9]. Common findings include symmetric involvement of all limbs decreased muscle mass, shortness of the affected limb, fixed or flexible joint contractures, and dimples over the affected joints [9–11]. Unless there is concomitant birth asphyxia, mental development is normal [11]. Babies commonly are in breach position or in unusual positioning in utero requiring a C-section [9]. Ten percent have perinatal long bone fractures related to in utero disuse osteopenia [9]. In affected limbs, sensation is intact, and reflexes are diminished [10]. Muscle biopsies showed fatty-fibrous replacement within limb muscles interspersed with normal muscle (unless lack of mobilization had led to disuse atrophy and fiber disproportion) [10].

Common Physical Findings

Jaw—spared
Shoulders—internally rotated, adducted
Elbows—fully extended and fixed
Forearms—pronated
Wrists—fixed in flexion
Hands—partially flexed fingers (i.e., flexion creases of palm and finger not fully formed), partial absence of fingers and toes
Trunk—spared
Spine—may be involved
Hips—15% dislocated, fixed in flexion or extension, adducted or abducted
Knees—fixed in extension or flexion
Feet—equinovarus adduction, other foot deformities occur [9–11].

Common Associated Findings

Children with amyoplasia can have midline facial hemangiomas and a round facial appearance. Muscle defects in the abdominal wall and inguinal hernias occur in about 10% of children with amyoplasia [11]. Gastroschisis and bowel atresia are also associated findings [10, 11].

Distal Arthrogryposis

There are presently ten different clinical forms of Distal Arthrogryposis (DA) characterized by distal joint involvement, limited proximal joint involvement, autosomal dominant inheritance, autosomal recessive, and sporadic genetic causes [9, 11].

DA is defined as an inherited primary limb malformation disorder characterized by congenital contractures of two or more different body areas and without primary neurological and/or muscle disease that affects limb function [11]. The 3 most common forms of DA are DA Type 1, DA Type 2A, and DA Type 2B [9].

DA Type 1

- Mainly distal joint involvement, no facial or other organ system involvement [9]
- Clenched fists at birth, ulnar deviation, medially overlapping fingers, and club feet or other foot malpositions [11]
- Hips may be affected, calves small, and opening of the mouth mildly limited [11]

DA Type 2A (Freeman-Sheldon Syndrome)

- Facial contractures, small "whistling" mouth [9, 11]
- Short stature, scoliosis, mainly distal joint but varying proximal joint involvement [9, 11]

DA Type 2B (Sheldon-Hall Syndrome)

- Intermediate form between DA1 and DA2A with milder facial involvement and mainly distal joint involvement [9, 11]
- Vertical talus, ulnar deviation, severe camptodactyly, triangularly shaped face, prominent nasolabial folds, down slanting palpebral fissures, small mouth, and prominent chin [11]
- Foot deformities may be asymmetric [11]

Radiographic Studies/Testing/Evaluation

Photographs can document limb positioning at rest

Providers and physical therapist assessments include range of motion of each joint for each limb documenting end range at baseline. Serial assessments denote improvement with treatment or regression or progression of contractures over time.

Imaging studies:

- Radiographs to evaluate bony abnormalities (assess bones, fusions, extra or missing carpals/tarsals, disproportionate issues, short stature, scoliosis, absence of the patella, humeroradial synostosis).
- Ultrasounds to assess CNS, hips, visceral anomalies, muscle tissue.
- If differentiating myopathic versus neuropathic conditions; skin or muscle biopsies, electromyography and nerve conduction (EMG/NC) studies may be useful [6].

Treatment/Management

- Initiate stretching of joint muscle contractures, especially first 3–4 months of life, by way of educating family on passive range of joint motion stretches and involving physical therapy [4, 11]. Manipulation of deformities started soon after birth can improve ROM, can preserve and enhance muscle growth, and may remove or decrease the need for surgery [11]
- Immobilization with nighttime splinting and short periods of serial casting can slow down the recurrence of deformities but should be minimized to avoid further muscle atrophy [4, 11]
- Muscle function is more important than severity of joint contractures for the prediction of walking ability and functional level [11]
- Pediatric physiatrist should help direct the overall management of the child [4]
- Preservation of childhood experiences and family structure may be more important than limited function or care gains [4]

Upper Extremities

Goal of treatment, therapy, splinting, use of adaptive equipment, and surgical contracture releases if needed for self-help skills/independence in activities of daily living (ADLs). Evaluate overall function versus specific joints [8].

Elbows

Goals: passive and active flexion (i.e., for feeding) and active extension (to reach for toileting), ability to use assistive devices, and self-transfers [8].

Fingers

Goals: passive and active flexion and extension of fingers and thumbs to grasp objects for ADLs increase ability to be independent. Many patients adapt despite dexterity problems, with/without the use of assistive devices. Soft tissue releases or surgical interventions may be necessary for severe deformities or to assist with thumb/palm oppositional improved grasp [8].

Spine

The spine is affected in about one-third of arthrogryposis patients, thus monitoring for scoliosis is recommended and if identified referral to spine specialist to address if progressive, curves in this population respond poorly to orthosis. Corrective surgery may be necessary [8].

Hip

Contracture releases maybe be needed for ambulation if hip flexion contractures are greater than 45°. Closed reduction generally unsuccessful in achieving long term-stable reduction. Osteotomy, open reduction are associated with complications such as hip stiffness, repeat dislocation, subluxation, and avascular necrosis [4].

Knee

Goal of therapy and splinting is to optimize knee flexion for sitting but not lose passive extension for standing (ideal less than 20° flexion contraction, a least 60° of passive flexion). Hyperextension responds well to therapy or splinting. Knee dislocations should be reduced early and will require surgery. Age 1–3 months, percutaneous quadriceps tenotomy with serial casting has been successful. Later treatment will require more soft tissue, capsulotomy, ligament resection, or bony procedures [4].

Foot

For talipes equinovarus (club foot) treatment, casting and surgery with complete correction are typically not achieved [4].

Clinical Vignette

Female 16 years of age with arthrogryposis.

Birth History

Limited birth & developmental history: Received early intervention services, began walking at age 2.5 years. Past splinting with nighttime ankle-foot orthoses (AFOs).

Past Medical History

Bilateral dysplasia of hips (shallow acetabula with hips displaced laterally and superiorly with 60–70% uncovered) patellar subluxation/dislocation.

Past Surgical History

Right Dega acetabuloplasty with allograft wedges, bilateral hip arthrogram at age 5.

Social History

Lives with parents and sibling. Patient attends high school, exempt from physical education, swims competitively.

Independent w/all activities of daily living (ADLs), ambulates in the community moderate distances with AFOs without external support, otherwise uses light weight wheelchair.

Physical Exam

Short stature, normal BMI, bilateral calf atrophy, ROM abnormalities: hips with limited flexion, abduction, and greater external rotation than internal rotation bilaterally. Full knee extension and adequate knee flexion. Limited ankle dorsiflexion with knees flexed and extended. Bilateral stiff knee, positive Trendelenburg gait, legs in external rotation with exaggerated foot progression angles.

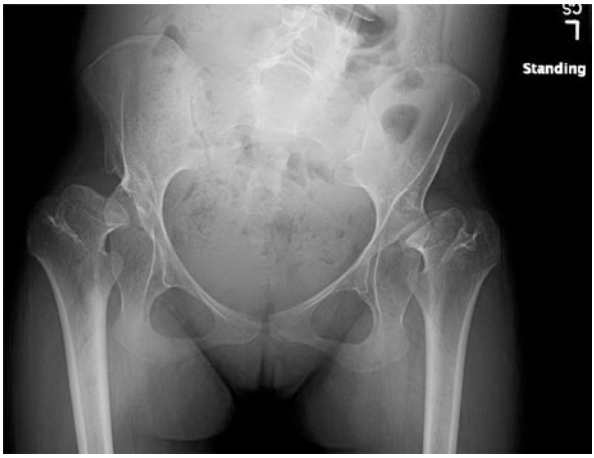


Fig. 18.1 Arthr hip (Adolescent with arthrogryposis—recent pelvis X-ray)

Radiographic Exam

*AP Pelvis: historic; chronic loss of height of each femoral head, with associated widening of each femoral neck. Dysplastic acetabulum with superior lateral subluxation of each femoral head relative to its respective acetabulum, right worse than left. Mild right superior pelvic tilt. (*Fig. *18.1).*

Current Therapeutic Program

Promote functional activities, balance of exercise, and avoidance of aggravating activities for hip conservation. School accommodations. Conservative management for pain. Intermittent PT to maintain ROJM, stretching & home exercise program. Monitor skin with use of splints. Transitional skills & counseling for patient/family, education for hip replacement as a young adult.

Clinical Pearls

The multidisciplinary treatment team typically includes pediatric neurologist and geneticist (help to determine the underlying condition especially if CNS involvement and prognosis), pediatric orthopedic surgeon, orthopedic hand surgeon, physiatrist, occupational therapist, physical therapist, and orthotist with coordination of patient care shared among all caregivers. All are involved in the assessment of a patient's current functioning, identification of patient/family goals; coordination of multiple treatments for contracture management, consideration and timing of

orthopedic surgical interventions (contracture releases, dislocation correction/procedures) that may improve their abilities, determination of use of braces/splints to maintain corrective joint/limb post-operative positions, and equipment that may aid in independent functional activities, ambulation, and successful outcomes [12].

Natural History, Primary and Secondary Prevention

Amyoplasia

- Contractures in children with amyoplasia are at their maximum at birth [11]
- Some contractures spontaneously improve [4]
- Some individuals with amyoplasia had early feeding problems which resolved by 4 months of age. It is unclear if this is related to decrease in ability to suck or delayed coordination of intestinal peristalsis [10]
- The long-term outcome for patients with amyoplasia is still unclear [10]
- Arthritis in affected joints did occur in the mid-20s. This was likely related to periarticular and "corner" fractures occurring because of vigorous physical therapy (which is essential) at earlier ages [10]
- Degenerative knee arthritis is more commonly associated with extension deformities [4]

References

1. Ferguson J, Wainwright A. Arthrogryposis. Orthopaed Trauma. 2013;27(3):171–80.
2. Ambegaonkar G, Manzur AY, Robb SA, Kinali M, Muntoni F. The multiple phenotypes of arthrogryposis multiplex congenita with reference to the neurogenic variant. Eur J Paediatr Neurol. 2011;15(4):316–9.
3. Hoff JM, Loane M, Gilhus NE, Rasmussen S, Daltveit AK. Arthrogryposis multiplexa congenita: an epidemiologic study of nearly 9 million births in 24 EUROCAT registers. Eur J Obstetr Gynecol Reproduct Biol. 2011;159(2):347–50.
4. Song K. Lower extremity deformity management in amyoplasia: when and how. J Pediatr Orthoped. 2017;37(Suppl 2):S42–s7.
5. Tjon JK, Tan-Sindhunata GM, Bugiani M, Witbreuk MM, van der Sluijs JA, Weiss MM, et al. Fetal akinesia deformation sequence, arthrogryposis multiplex congenita, and bilateral clubfeet: is motor assessment of additional value for in utero diagnosis? A 10-year cohort study. Prenat Diagn. 2019;39(3):219–31.
6. Chen H. Atlas of genetic diagnosis and counseling. 2nd ed. New York: Springer-Verlag; 2012.
7. Donker ME, Eijckelhof BH, Tan GM, de Vries JI. Serial postural and motor assessment of Fetal Akinesia Deformation Sequence (FADS). Early Hum Dev. 2009;85(12):785–90.
8. Sarwark JFL, Cynthia R. Pediatric orthopaedics and sports injuries: a quick reference guide. 2nd ed. American Academy of Pediatrics; 2014.
9. Hall JG, Kimber E, van Bosse HJP. Genetics and classifications. J Pediatr Orthoped. 2017;37(Suppl 1):S4–s8.

10. Hall JG, Aldinger KA, Tanaka KI. Amyoplasia revisited. Am J Med Genet Part A. 2014;164a(3):700–30.
11. Kimber E. AMC: amyoplasia and distal arthrogryposis. J Children's Orthopaed. 2015;9(6):427–32.
12. Villard L, Nordmark-Andersson E, Crowley B, Straub V, Bertoli M. Multidisciplinary clinics. J Children's Orthopaed. 2017;37(Suppl 1):S29–s30.

Chapter 19
Larsen Syndrome

Bensen B. Fan

Description/Background of the Disorder: Brief Overview of Conditions

In 1950, Dr. LJ Larsen described a congenital skeletal dysplasia associated with characteristic flat facial features and multiple dislocations of major joints such as the knees, hips, and elbows [1]. In his cohort of six patients presenting to the San Francisco Shriner's Hospital, Dr. Larson noticed a characteristic pattern of flat facies and multiple major joint dislocations [1]. The most notable joint dislocations were anterior knee dislocations, where the tibia was displaced anterior to the femur. Furthermore, these patients had dislocations of both hips, elbows, and equinovarus or equinovalgus feet. The typical facial features included wide-spaced eyes, prominent forehead, and depressed nasal bridge [1]. Patients' hands had characteristic cylindrical fingers that do not taper towards the tips, short metacarpals, and spatulate thumbs. The patients had normal mentation [1]. In contrast to arthrogryposis or muscular dystrophy, muscle biopsy for Larson's syndrome was negative. Family history was often negative, and siblings were normal.

Epidemiology/Pathophysiology

Larsen syndrome is estimated to be present in 1 in 10,000 births [2]. Usually diagnosed shortly after birth based on characteristic features, this syndrome oftentimes results from a sporadic autosomal dominant mutation [3, 4], but there are also

B. B. Fan (✉)
Department of Orthopaedic Surgery, Children's Hospital of Los Angeles, Los Angeles, CA, USA

Atlantic Medical Group, Goryeb Children's Hospital, Morristown, NJ, USA

J. F. Sarwark, R. L. Carl (eds.), *Orthopaedics for the Newborn and Young Child*,
https://doi.org/10.1007/978-3-031-11136-5_19

recessive inheritances [5, 6]. In the autosomal dominant pattern, there is a filamin B mutation, which is involved in intracellular protein scaffolding/signaling and protein trafficking, affecting the development of growth plate and vertebrae [3, 5].

In the autosomal recessive pattern, there is a carbohydrate sulfotransferase three mutation, affecting glycosaminoglycan (GAG) processing, which deregulates joint and spine development [5, 6].

There are case reports of unilateral Larsen syndrome, in which only one side of the body is affected, pointing to a somatic-mosaic mutation [5, 7, 8].

Common Clinical Presentation: History and Physical

Larsen syndrome will be diagnosed at birth, or shortly afterwards, when the pediatrician or geneticist will notice certain characteristic features [1, 5, 9] (Fig. 19.1). Starting at the head, the baby will have a flattened nasal bridge producing a flat face [8–10]. There will be a broad forehead and hypertelorism [1, 9]. Occasionally, there may be cleft palate present [1].

Fig. 19.1 General appearance of Larsen syndrome patient. Flat face, wide-set eyes, tracheostomy present due to tracheomalacia, hyperextended knees (knee dislocation), and equinovarus or valgus feet

On physical exam, there will be generalized ligamentous laxity and anterior knee dislocation, in which the knees appear hyperextended [1, 9–11]. There will also be bilateral club feet (equinovarus feet or equinovalgus feet) [1, 9, 10]. While more obvious on X-ray than physical exam in a newborn, some patients will have bilateral hip dislocations and stiff elbows (bilateral ulnohumeral dislocation and radioulnar synostosis) [1, 5, 8–10].

Patients with Larsen syndrome presenting to the pediatrician's office 2–3 years after birth will have normal mental status and IQ [1]. Some patients will have begun to sit by 6 months and stand and speak words by 12 months [1]. Despite these normal developments, they will still have bilateral dislocated knee and hips and equinovarus or equinovalgus feet. They will display characteristic facies, wide thumbs, and cylindrical fingers [1, 9, 10].

If a child presents with fatigue and increased sitting during games, a c-spine X-ray should be obtained to look for c-spine instability that is causing cervical myelopathy [12–14].

Radiographic Studies/Testing/Evaluation

Once a working diagnosis of Larsen syndrome is made, a skeletal survey will identify major joint dislocations such as bilateral shoulder dislocations, ulnohumeral elbow dislocations, and radioulnar synostosis in the upper extremity [1, 5, 8, 9] (Figs. 19.2 and 19.3). In the lower extremity, skeletal survey will identify bilateral hip dislocations and anterior knee dislocations (Figs. 19.4 and 19.5). Depending on how long the patient's joints have been dislocated, there may be changes such as flattened femoral condyles or increased posterior tibial slope [1].

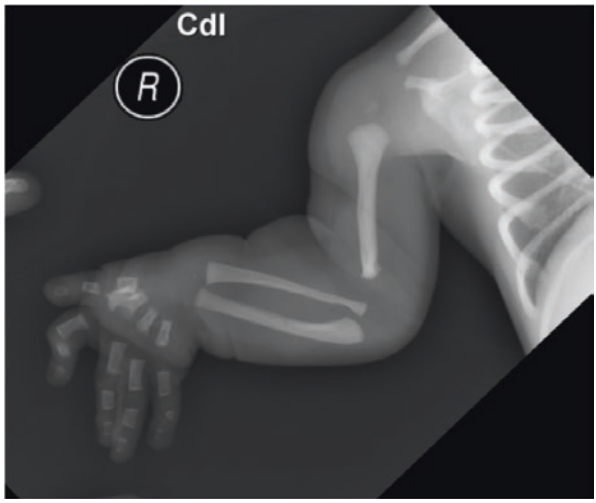


Fig. 19.2 X-ray of the right arm showing dislocation of the shoulder and elbow. Used with permission from The Children's Orthopaedic Center at Children's Hospital Los Angeles

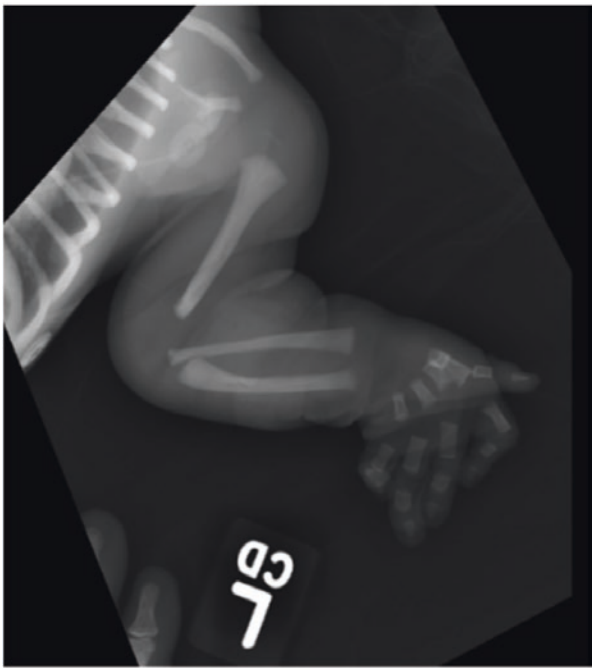


Fig. 19.3 X-ray of the left arm showing dislocation of the shoulder and elbow. Used with permission from The Children's Orthopaedic Center at Children's Hospital Los Angeles

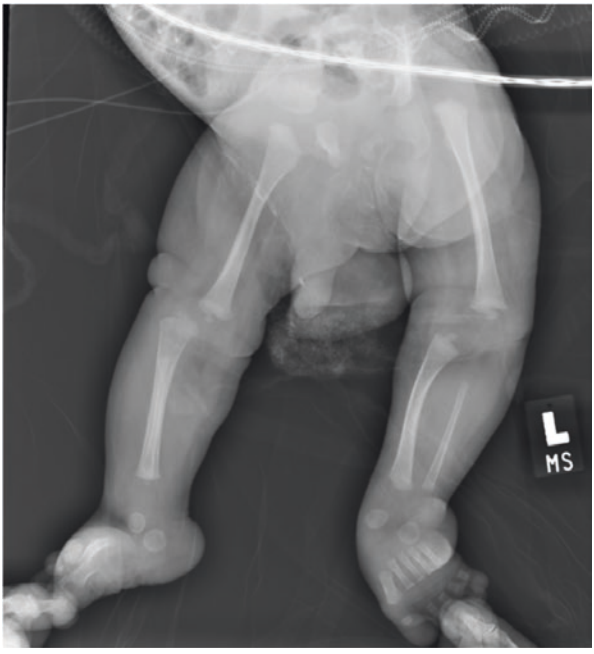


Fig. 19.4 X-ray of lower extremities showing bilateral dislocated hips and anterior dislocation of tibia on femur (knee). Used with permission from The Children's Orthopaedic Center at Children's Hospital Los Angeles

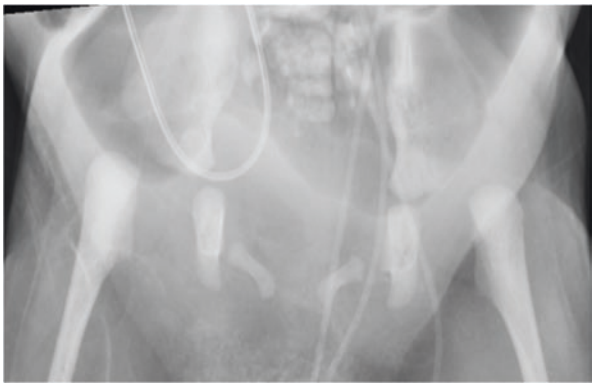


Fig. 19.5 X-ray of the pelvis showing bilateral dislocated hips. The femurs are more proximal than normal. The femoral heads (which are not ossified yet) should be pointing towards the tri-radiate cartilage. Used with permission from The Children's Orthopaedic Center at Children's Hospital Los Angeles

Radiographs of the hands and feet may show extra ossification centers. A "bifid calcaneus" or a double ossification center in the calcaneus is common in Larsen syndrome [10].

An X-ray or other imaging of the cervical spine should be obtained prior to a patient's first birthday to look for structural instability or hypoplasia of the vertebral bodies that would contribute to developing cervical myelopathy [12, 14].

A knee arthrogram (or MRI) will show an absent suprapatellar pouch, misaligned patella, and possibly an absent anterior cruciate ligament [5, 15] (Figs. 19.2, 19.3, 19.4, and 19.5).

Treatment/Management

The critical management concern in a patient with Larsen syndrome is the airway. Their first-year mortality is 40%, but there is a good prognosis if they can survive the first year of life [5, 12].

Death is a result of soft cartilage supporting larynx and trachea, and elasticity of the thoracic cage and costochondral junction, contributing to upper airway respiratory failure [12, 16, 17]. There are also described cases of congenital septal defects in the heart, elongation of aorta, and mitral valve lesions similar to those found in Marfan's disease [5, 18, 19].

Once the patient is medically stable, the foot deformities can be treated with serial casting. Sometimes a foot brace may be necessary if there is ankle instability [5].

Manipulation of the knees may be attempted to achieve some flexion, but it is rarely successful and distal femur fractures can result from overly aggressive manipulation [5, 15]. Once knee dislocations are confirmed with no benefit of improvement with casting, manipulation can be abandoned. Surgical open reduction of knees can be performed as early as 3–4 months with possible femoral shortening osteotomies if necessary to reduce the joint. The most important part of treating the dislocated knees is stability in extension [5, 11, 15, 20–23]. This allows activation of the quadriceps muscle, a future ACL reconstruction, and application of a long-term orthosis.

Treatment of hip dislocation results in a high re-dislocation rate. Just like in arthrogryposis, it is recommended the hips are treated after 1 year old so that pelvic and femoral osteotomies can be performed as needed [5] after appropriate indication. Knee dislocations needed to be treated prior to or simultaneous with hip dislocations because the hips are casted with knees in flexion.

Usually, the upper extremities are asymptomatic despite dislocated shoulders and elbows [12]. Occasionally surgeons may advise splint equipment for the arms to help with range of motion, but rarely will the patient require upper extremity surgery [12].

It is critically important to obtain a cervical spine X-ray prior to a patient's first year of life to rule out cervical kyphosis [14]. If the curve is still flexible, the patient may be treated with posterior only fusion and halo ring application for stability while the fusion mass heals [24]. If the patient is severely kyphotic and has myelopathy, an anterior decompression with circumferential fusion is necessary [24].

Finally, the surgical team should be aware of possible anesthesia complications from a mobile in-folding arytenoid cartilage that creates an airway blockage [5, 16, 17].

Clinical Vignettes/Clinical Pearls

As a review, physicians diagnosing patients with Larsen syndrome should be aware of C-spine instability/myelopathy, airway problems, and tracheomalacia. A cervical spine X-ray should be obtained prior to 1 year old [12–14, 24].

The dislocated knees often have an absent ACL, patella misalignment. Over manipulation can result in a distal femur fracture and should be abandoned if there is little improvement after 1 month [5, 9].

Natural History, Primary and Secondary Prevention

Patient's with Larsen syndrome have normal intelligence [1]. As such, functional treatment of their orthopedic conditions can help them achieve maximal function and perform activities of daily living. There is a 40% chance that they will die of respiratory failure in their first year of life [12]. Physicians should be aware of airway compromise and rule out cervical spine instability and myelopathy at an early stage. Even after reduction of dislocated joints, there may be bony deformity from long standing dislocation.

References

1. Larsen LJ, Schottstaedt ER, Bost FC. Multiple congenital dislocations associated with characteristic facial abnormality. J Pediatr. 1950;37(4):574–81.
2. Bonaventure J, Lasselin C, Mellier J, Cohen-Solal L, Maroteaux P. Linkage studies of four fibrillar collagen genes in three pedigrees with Larsen-like syndrome. J Med Genet. 1992;29(7):465–70.

3. Zhang D, Herring JA, Swaney SS, McClendon TB, Gao X, Browne RH, et al. Mutations responsible for Larsen syndrome cluster in the FLNB protein. J Med Genet. 2006;43(5):e24.
4. Vujic M, Hallstensson K, Wahlstrom J, Lundberg A, Langmaack C, Martinson T. Localization of a gene for autosomal dominant Larsen syndrome to chromosome region 3p21.1-14.1 in the proximity of, but distinct from, the COL7A1 locus. Am J Hum Genet. 1995;57(5):1104–13.
5. Benjamin AA, Goldberg MJ. Chapter 8: Syndromes of orthopaedic importance. In: Stuart Weinstein JF, editor. Lovell and winter's pediatric orthopaedics. 7th ed. Philadelphia, PA: Lippincott Williams and Wilkins; 2014.
6. Hermanns P, Unger S, Rossi A, Perez-Aytes A, Cortina H, Bonafe L, et al. Congenital joint dislocations caused by carbohydrate sulfotransferase 3 deficiency in recessive Larsen syndrome and humero-spinal dysostosis. Am J Hum Genet. 2008;82(6):1368–74.
7. Frints SG, De Smet L, Fabry G, Fryns JP. A young female with asymmetric manifestations of larsen syndrome: another example of unilateral somatic cell-line mosaicism. Clin Dysmorphol. 2000;9(4):273–6.
8. Bicknell LS, Farrington-Rock C, Shafeghati Y, Rump P, Alanay Y, Alembik Y, et al. A molecular and clinical study of Larsen syndrome caused by mutations in FLNB. J Med Genet. 2007;44(2):89–98.
9. Latta RJ, Graham CB, Aase J, Scham SM, Smith DW. Larsen's syndrome: a skeletal dysplasia with multiple joint dislocations and unusual facies. J Pediatr. 1971;78(2):291–8.
10. Steel HH, Kohl EJ. Multiple congenital dislocations associated with other skeletal anomalies (Larsen's syndrome) in three siblings. J Bone Joint Surg Am. 1972;54(1):75–82.
11. Curtis BH, Fisher RL. Heritable congenital tibiofemoral subluxation. Clinical features and surgical treatment. J Bone Joint Surg Am. 1970;52(6):1104–14.
12. Goldberg M. In: David Skaggs JF, editor. Staying out of trouble in pediatric orthopaedics. Philadelphia, PA: Lippencott Williams and Wilkins; 2006.
13. Johnston CE 2nd, Birch JG, Daniels JL. Cervical kyphosis in patients who have Larsen syndrome. J Bone Joint Surg Am. 1997;78(4):538–45.
14. Johnston CE 2nd, Schoenecker PL. Cervical kyphosis in patients who have Larsen syndrome. J Bone Joint Surg Am. 1997;79(10):1590–1.
15. Matar HE, Garg NK. Management of joint dislocations of the lower limb in Larsen syndrome: practical approach. Ann R Coll Surg Engl. 2017;99(1):e8–e10.
16. Malik P, Choudhry DK. Larsen syndrome and its anaesthetic considerations. Paediatr Anaesth. 2002;12(7):632–6.
17. Tobias JD. Anesthetic implications of Larsen syndrome. J Clin Anesth. 1996;8(3):255–7.
18. Kiel EA, Frias JL, Victorica BE. Cardiovascular manifestations in the Larsen syndrome. Pediatrics. 1983;71(6):942–6.
19. Liang CD, Hang CL. Elongation of the aorta and multiple cardiovascular abnormalities associated with larsen syndrome. Pediatr Cardiol. 2001;22(3):245–6.
20. Abdelaziz TH, Samir S. Congenital dislocation of the knee: a protocol for management based on degree of knee flexion. J Child Orthop. 2011;5(2):143–9.
21. Curtis BH, Fisher RL. Congenital hyperextension with anterior subluxation of the knee. Surgical treatment and long-term observations. J Bone Joint Surg Am. 1969;51(2):255–69.
22. Oetgen ME, Walick KS, Tulchin K, Karol LA, Johnston CE. Functional results after surgical treatment for congenital knee dislocation. J Pediatr Orthop. 2010;30(3):216–23.
23. Saleh M, Gibson MF, Sharrard WJ. Femoral shortening in correction of congenital knee flexion deformity with popliteal webbing. J Pediatr Orthop. 1989;9(5):609–11.
24. Sakaura H, Matsuoka T, Iwasaki M, Yonenobu K, Yoshikawa H. Surgical treatment of cervical kyphosis in Larsen syndrome: report of 3 cases and review of the literature. Spine (Phila Pa 1976). 2007;32(1):E39–44.

Chapter 20
Amniotic Band Syndrome

Miranda De Loof and Diane Dudas Sheehan

Brief Overview of Condition

Amniotic Band Syndrome (ABS) refers to a complex spectrum of asymmetric congenital anomalies with a **triad** of characteristic features:

1. Distal ring constrictions associated with fibrous bands (with or without peripheral neurovascular disorder)
2. Acrosyndactyly of the fingers and/or the toes
3. Intrauterine limb and digital amputations

Rarely, the malformation disorder may also be characterized by major anomalies of the craniofacial region and body wall complex and associated with vascular abnormalities [1–4].

ABS is the most common terminal congenital malformation of a limb [3, 5, 6].

The nomenclature of ABS includes amniotic band sequence, congenital constriction band syndrome (CBS), Streeter's dysplasia, Simonart's bands, amniotic band disruption complex, congenital annular defects, congenital ring constrictions, ADAM (Amniotic Deformity, Adhesion, Mutilations) complex, TEARS (The Early Amnion Rupture Spectrum) of defects, fetal disruption complex, annular ring constriction, annular groove, intrauterine amputation [2, 3].

M. De Loof
Division of Orthopaedic Surgery and Sports Medicine, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA
e-mail: MDeLoof@luriechildrens.org

D. D. Sheehan (✉)
Division of Orthopaedic Surgery and Sports Medicine, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA

Department of Physical Medicine and Rehabilitation, Northwestern University Feinberg School of Medicine, Chicago, IL, USA
e-mail: DSheehan@luriechildrens.org

J. F. Sarwark, R. L. Carl (eds.), *Orthopaedics for the Newborn and Young Child*,
https://doi.org/10.1007/978-3-031-11136-5_20

Background, Epidemiology, and Pathophysiology

Over the centuries theorists: Montgomery, Torpin, and Higginbottom proposed the pathogenesis of ABS with associated abnormal prenatal history, yet this still does not explain a portion (up to 40%) of occurrences. Streeter's oppositional view suggested an inherent developmental defect in embryogenesis. Pathophysiology of ABS still remains uncertain, however probably heterogeneous including extrinsic factors (exogenous to the fetus that is secondarily involved) and a genetic relationship (intrinsic fetal anomaly) [3]. The birth defects seen in ABS are likely caused by a partial rupture of the amniotic sac in the early stage of pregnancy, low amniotic fluid level, and floating fibrous amniotic strands which entangle body parts, limbs, and appendages of the fetus, constrict blood circulation, and cause auto-amputation of digit or limb, tissue necrosis with some healing in utero. The nature and severity of resulting deformities are related to the timing and initiating event of amniotic rupture and may be associated with intrauterine infection [7]. Extrinsic compression from deep amniotic bands interferes with limb artery development causing vascular supply anomalies fairly proximal to the band or amputation in approximately 60% of the cases [4]. Direct pressure from the compression band can cause progressive swelling, compartment syndrome, and attributable neurologic impairment [3]. A subset of cases manifest with associated birth defects including: cranial and facial anomalies, nasal deformity, cleft lip and palate (CLP), neural tube defects, meningocele, congenital heart defect, renal anomalies, club foot, polydactyly, supernumerary nipples, and skin tags, thus suggesting a genetic origin [3, 8].

ABS is rare with a prevalence of 0.9 per 10,000 births with an associated infant mortality of 4.6% and perinatal mortality of 12.7% [1]. ABS is sporadic in nature with no specific genetic evidence or familial hereditary features found [1, 5, 7, 9]. There is no sex predilection with an equal distribution, 1:1 male to female ratio [1, 5].

Prenatal risk factors associated with ABS include prematurity, low birth weight (LBW), maternal illness during pregnancy, maternal drug exposure, maternal hemorrhage/trauma, and a higher incidence in first pregnancies [1, 2].

Differential diagnosis includes acquired raised bands of infancy, infantile garment (sock-line) bands, nevus lipomatous superficialis, smooth muscle hamartoma, and Michelin tire baby [10].

Clinical Presentation: History and Physical

Clinical manifestations of ABS are characterized by specific fetal malformations which usually facilitate its diagnosis with anomalies commonly present in the distal or peripheral part of the extremities [3, 11]. The most common clinical findings include constriction rings, acrosyndactyly, and intrauterine amputations [3, 11].

- Constriction rings are usually linear, perpendicular limb bands; they may be partial or completely circumferential, and may result in a partial deformity, or total amputation of the affected structures [5].
- Constriction rings can vary in terms of the depth and width of the groove, as well as the number of rings present in the affected extremity.
- Superficial or shallow constriction rings tend to affect the skin and subcutaneous tissues only.
- Deeper constriction rings (deep indentations of the skin) usually extend to the fascia and may reach the bone. Deeper rings have a greater risk of involvement of other anatomical structures such as lymph vessels, arteries, veins, nerves, and tendons [11].
- Soft tissues and skeletal structures proximal to the constriction rings are typically normal, with the severity of the deformity of one limb independent of another [3].
- Constriction rings that involve the upper extremities have a tendency to affect the central digits more so than the thumb or the small digit [3].
- Constriction rings affecting digits result in phalangeal hypoplasia, malformed digits, and distal amputations. Phalangeal growth centers can be injured if the constriction ring is in close proximity, leading to digit and nail hypoplasia [11].
- In the foot, the great toe is most commonly involved [3, 11].
- Acrosyndactyly results from in utero entanglement of the previously separated digits with the amniotic fibrous bands, causing the digits to refuse during development. Cutaneous syndactyly of adjacent fingers with a lassoed appearance, and sinus tracks between the digits are usually present proximally [3].
- When the constriction ring is severe enough that reaches the bone, amputations of the affected extremity ensue. The lack of blood supply to the developing limb results in an in utero transverse amputation. In most cases, the amputation results in the loss of hand digits or toes, however, more severe amputations of the limbs may result in congenital tibial pseudoarthrosis or below knee amputations, which are less common [11].
- In cases of intrauterine digit amputation, the digit may undergo in utero resorption; be present at delivery as a loose entity; or engraft itself elsewhere on the fetus [11].
- Club foot deformity (congenital talipes equinovarus) is the most common additional abnormality, which can be idiopathic or rigid. The rigid type is usually the result of compression of the peroneal nerve (direct damage to evertor muscles) by a constriction band affecting that extremity [2, 3, 11].
- Distal swelling and lymphedema may or may not be present as a result of a constriction ring affecting the digits.
- Additional clinical findings that are commonly seen with ABS include phalangeal hypoplasia, lymphedema, leg length discrepancies [3]. Other associated but less common conditions include metatarsus adductus, peripheral nerve palsy, dystrophic nails, postnatal gangrene, cleft lip and palate, skin-tube pedicles, dislocated hip, visceral body wall malformations, and craniofacial synostosis defects [3].

Key Points/Pearls

- The lack of thumb involvement is likely due to the fetus holding the thumb in tight adduction and flexion during intrauterine life, making the entanglement less likely [11]. Other theories have proposed that the sparing of the thumb is the result of the progression of in utero development of each ray, with the thumb preceding the central digits [2].
- Severe lymphedema (uncompressible), distal from the ring is considered a surgical emergency. Even in surgically repaired limbs, capillary refill may be decreased, and acral temperatures may be lower than the unaffected limb, as a result of neurovascular and lymphatic compromise [11].

Physical examination may reveal (see Figs. 20.1, 20.2, and 20.3):

- Hourglass deformity of affected limb
- Complete or partial constriction rings; superficial or deep fibrous bands
- Single or multiple bands
- Edema of structures distal from the ring
- Acrosyndactyly, digit hypoplasia
- Partial or total auto-amputation of structures
- Intrinsic muscle atrophy; decreased thenar/hypothenar eminences for constriction rings affecting the upper limbs
- Decreased muscle tone
- Nerve dysfunction (sensory and motor); clawing of digits/inability to extend digits; flexion contractures of digits; decreased light touch sensation and two-point discrimination

Key Point/Pearl

- Physical examination should include a complete neurologic evaluation, even in the infant, to determine extent of nerve involvement (sensory and motor)

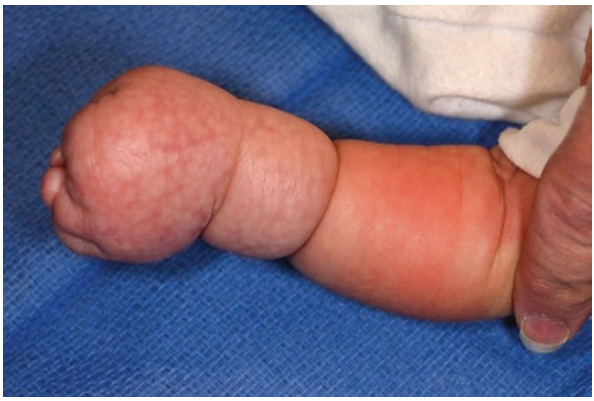


Fig. 20.1 Dorsal UE. Photo by Paul Berg, Lurie Children's Hospital

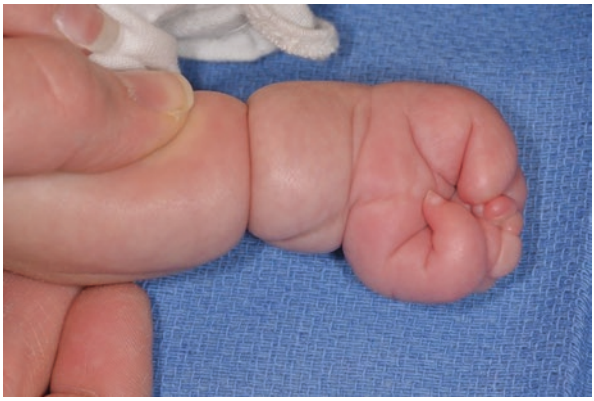


Fig. 20.2 Volar UE. Photo by Paul Berg, Lurie Children's Hospital

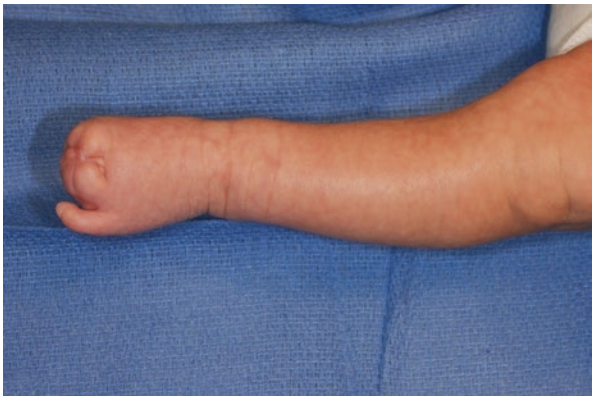


Fig. 20.3 LE. Photo by Paul Berg, Lurie Children's Hospital

Radiographic Studies/Testing/Evaluation

Prenatal diagnosis is usually possible during the second and third trimesters (diagnosis during the first trimester is extremely difficult) [3]. Prenatal serial ultrasonography detects the main ABS features, restriction of motion, and the constriction bands around the limbs [7].

Key Point/Pearl
The diagnosis of ABS should not be solely made based on the presence of amniotic sheets or bands. In some instances, chorion or amnion bands are found in the uterine cavity but they have a free edge, which does not attach to the fetus. These sheets do not result in restriction of movement or fetal abnormalities. Thus, visualization of amniotic bands on ultrasonography only helps confirm the diagnosis of ABS, as long as the bands are attached to the fetus, and impair mobility or cause deformity [3].

Prenatal MRI may provide more detailed and precise diagnosis if there is a high suspicion of ABS and can help delineate the depth of the constriction band and the extent of the resultant lymphedema if present [7]. Magnetic resonance angiography (MRA) or computed tomographic angiography (CTA) can be used to study the arterial vasculature, especially if the constriction ring is deep, and surgical intervention is being considered [4].

Once the infant is born, radiographs can be used to evaluate affected bony structures.

Pre-operative, intra-operative, post-operative electromyography (EMG) and nerve conduction velocity studies (NCV) are usually indicated for deep constriction rings, to evaluate the effects of the rings on motor and sensory nerve function [9].

Children with limb defects need thorough evaluation of all organ systems [1]. Evaluate for craniofacial (oral cavity deformities such as cleft palate) and visceral deformities (such as cardiovascular abnormalities) [7, 12].

Gait analysis may be used for patients who have a leg length discrepancy as a result of ABS.

Classification Systems

Classification: There is no widely accepted classification scheme for ABS. Patterson's diagnostic criteria for congenital constriction rings (based on severity) are the most widely used in practice, since it is more relevant to the surgical methods [9].

Patterson (1961) [13]:

1. Simple ring constriction
2. Ring constrictions accompanied by deformity of the distal part, with or without lymphedema (most commonly seen)
3. Ring constrictions accompanied by fusion of distal parts ranging from fenestrated or terminal syndactyly to "exogenous" syndactyly
4. Intrauterine amputations

Hall (1982) [13]:

1. Mild constriction (no lymphedema)
2. Moderate constriction (lymphedema)
3. Severe constriction (amputation)

Weinzweig (1994) [13]:

1. Mild constriction (no lymphedema)
2. Moderate constriction with distal deformity, syndactyly, or discontinuous neurovascular or musculotendinous structures without vascular compromise
   (a) Without lymphedema
   (b) With lymphedema

3. Severe constriction with progressive lymphaticovenous or arterial compromise
   (a) Without soft tissue loss
   (b) With soft tissue loss
4. Intrauterine amputation [13]

Treatment/Management

Management of the patient begins with accurate diagnosis of ABS via serial prenatal ultrasonography (may include prenatal consultations with specialist prior to the infant's birth).

Refer infants/children to an orthopedic surgeon for evaluation. Neurosurgery and plastic surgery may also be necessary. Refer infants for early intervention services if any predication of functional deficits. Therapy and specialist referrals include: physical therapy, occupational therapy, orthotics/prosthetics, speech therapy if (craniofacial involvement).

Genetic counseling, not applicable (recurrence risk for patients sibling or offspring not increased) [13].

Given the variable presentations, treatment is highly individualized and in most instances requires staged procedures. Most surgical treatment takes place after birth, but given the advancement of prenatal radiodiagnosis, fetal surgery in utero, has been tried [7]. More complex plastic and reconstructive surgery takes into consideration the timing of the repair, to ensure maximization of limb function to allow the child to meet age-appropriate developmental milestones. At times, surgical intervention may need to be delayed to allow for increased limb growth and better understanding of the function of the affected structures. Superficial rings need no intervention, as long as they do not restrict lymph drainage and are not circumferential [5].

The main goals of treatment are aimed at maximizing function, improvement of limb function, and improvement of cosmetic appearance [5]. Discussions with family regarding management goals and expectations can begin in the prenatal period and should continue as the child grows.

More specific treatment goals include [11]:

- Separation of the digits and thumb to allow for unrestricted growth
- Maintenance of digit length and joint mobility, especially if affecting the thumb
- Improving appearance of contour deformity or "sand glass deformity"
- Well-padded, scar-free, amputation stumps

In utero surgery has been considered in the following cases:

- The severity of the band threatens fetal limb or fetal survival
- In utero band release will avoid progression of an ischemic insult, restoring limb anatomy and function

Key Point/Pearl
Fetal and maternal risks associated with in utero band release need to be thoroughly evaluated and discussed prior to any procedures.

Emergent postnatal surgery/neonatal period:

- Usually performed under local anesthesia while newborn is in the nursery
- Surgical procedure attempts to salvage the limb, prevent circulatory compromise, and decompress the bands.

One year of age:

- Separation of the digits, to allow for use of fingers during early development
- Decompression of swollen lymphedematous tissue

Corrective surgery:

- Excision of the constriction band in a one- or two-stage approach. The two-stage correction approach is usually reserved for complete circumferential bands, to minimize compromising the underlying neurovascular structures distally (one-half of the circumference of the constriction ring is excised; the other one-half is excised 3–6 months later) [5]. Two or more adjacent constriction rings usually require two-stage correction [9]. More recent studies have shown high successful rates with one-stage approach [9, 12].
- Lymphedema usually resolves within a few weeks of the first-stage constriction band release procedure; fasciotomy is considered if compartmental pressure is persistently elevated [12].
- Surgical techniques include Z-plasty, W-plasty, Sine plasty, Mutaf procedure, and direct closure [2, 12].
- Subcutaneous fat advancement flaps: mobilization of underlying fat beside the constriction ring to advance it over the tissue-deficient site; lipo-injection [5, 10].
- Additional approaches to the reconstruction include toe-to-hand transfers and distraction osteogenesis [12].
- Revisions are needed, especially if constriction band recurrence occurs, or there is poor post-operative appearance usually as the result of multiple Z-plasties [9].
- Nerve surgery: neurolysis, nerve decompression, compromised nerve segment excision, and nerve grafting may need to be considered if nerve palsies are present as a result of the constriction rings [6, 14].

Surgical complications include:

- Infection
- Edema
- Scarring; hypertrophic scars
- Maceration
- Graft loss
- Wound healing problems such as wound dehiscence, delayed wound healing
- Sensory loss; although difficult to distinguish from the initial insult caused by the constriction band
- Contractures; although difficult to distinguish from the initial insult caused by the constriction band
- Circulatory compromise
- Necrosis

Clinical Vignette

Female 15 years of age with amniotic band syndrome. Born with congenital right trans-tibial and right foot amputation, bony nubbin present (unknown origin), multiple constriction bands in the lower right leg, and malformation of third digit on left foot (minimal details of prenatal and birth history available).

Past Surgical History (Performed by Orthopedic and Plastic Surgeons)

- Release of distal amniotic bands with multiple Z-plasties at age 14-months.
- Modified Boyd osteotomy of distal right tibia and fibula at age 2.
- Guided growth (to improve medial knee tilt) with right proximal tibial hemi-epiphyseal (H) plating; along with resection of right distal tibia & fibula prominence for better prosthesis fit at age 10.
- Hardware (H-plate) removal at age 11.

Social History

Lives with family, in high school—plays Lacrosse, rides horses, and runs in track while using her prosthesis. Previously referred to prosthetics and physical therapy for gait training; has ongoing intermittent visits with orthopedist and the prosthetist.

Physical Exam

Well healed incisions/scars without erythema or drainage. At the terminal end of the right residual limb, mid tibial callous, no tenderness. No knee instability. In stance the pelvis fairly level, good knee alignment. Ambulates well with prosthesis.

Current Treatment Program

Promote independence in functional activities, yearly orthopedic assessment of residual limb and need for adjustments or new prosthetic system (see Figs. 20.4 and 20.5).

Natural History, Primary and Secondary Prevention

- Amniotic band syndrome is a rare and complex congenital malformation of a limb, difficult to diagnose given its unclear etiology.
- Primary prevention is not possible, although efforts should be made to minimize prenatal risk factors that have been associated with ABS.
- Given its variable presentation, treatment is highly individualized, does not allow for a standardized approach, and may require multiple and staged procedures as the child grows.

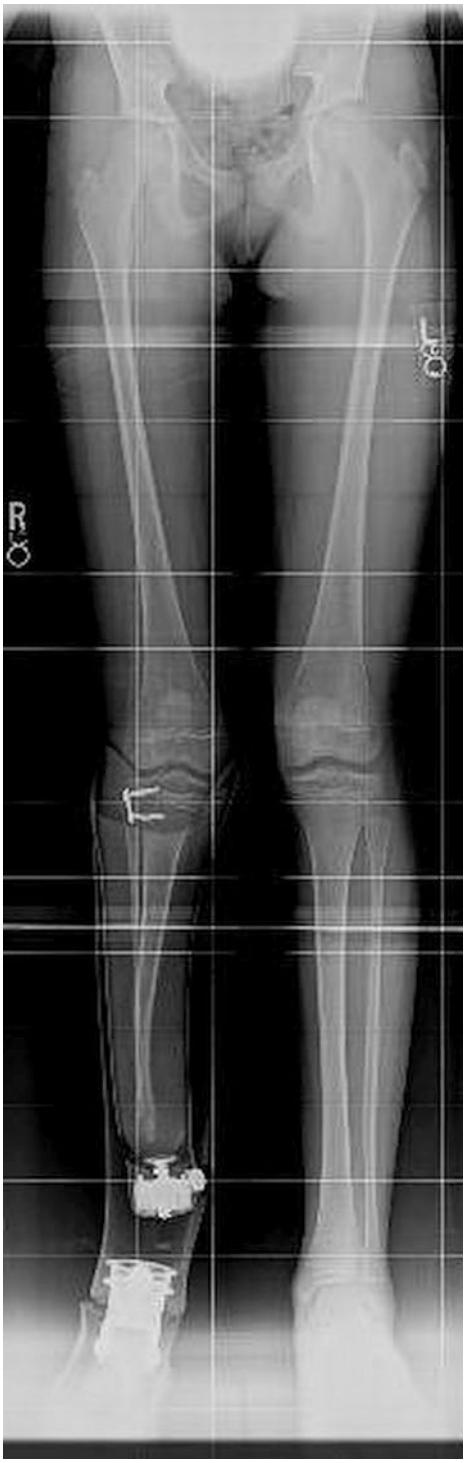


Fig. 20.4 Abs. legs. Standing legs image: pelvis fairly level with well seated hips within their respective well-formed acetabulum, normal femurs, normal left lower limb, H-plate in proximal tibia, short and tapered tibia/fibula with prosthesis in place

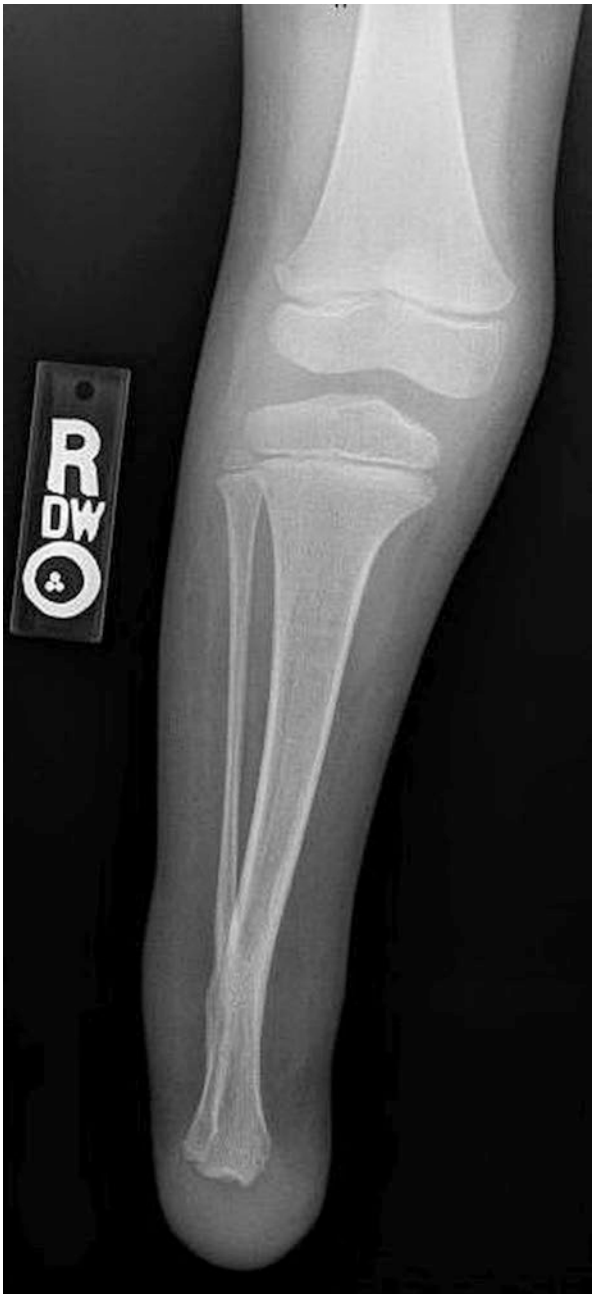


Fig. 20.5 Abs. tibia. Right lower limb congenital right trans-tibial and fibula amputation prior modified Boyd osteotomy s/p resection of right distal tibia and fibula

References

1. Koskimies E, Syvanen J, Nietosvaara Y, Makitie O, Pakkasjarvi N. Congenital constriction band syndrome with limb defects. J Pediatr Orthop. 2015;35(1):100–3.
2. Tada K, Yonenobu K, Swanson AB. Congenital constriction band syndrome. J Pediatr Orthop. 1984;4(6):726–30.
3. Walter JH Jr, Goss LR, Lazzara AT. Amniotic band syndrome. J Foot Ankle Surg. 1998;37(4):325–33.
4. Daya M, Makakole M. Congenital vascular anomalies in amniotic band syndrome of the limbs. J Pediatr Surg. 2011;46(3):507–13.
5. Choulakian MY, Williams HB. Surgical correction of congenital constriction band syndrome in children: replacing Z-plasty with direct closure. Can J Plast Surg. 2008;16(4):221–3.
6. Jones NF, Smith AD, Hedrick MH. Congenital constriction band syndrome causing ulnar nerve palsy: early diagnosis and surgical release with long-term follow-up. J Hand Surg. 2001;26(3):467–73.
7. Shetty P, Menezes LT, Tauro LF, Diddigi KA. Amniotic band syndrome. Indian J Surg. 2013;75(5):401–2.
8. Romero-Valdovinos M, Bobadilla-Sandoval N, Flisser A, Vadillo-Ortega F. The epithelial mesenchymal transition process may contribute to the pathogenesis of amniotic band syndrome. Med Hypotheses. 2014;83(3):306–11.
9. Jiang Y, Mao H, Yang X, Zhou S, Ni F, Xu Q, et al. Single-stage resection of type II constriction rings in limbs on the basis of histologic and magnetic resonance imaging observations: a retrospective study of 21 consecutive patients. Plast Reconstr Surg. 2016;138(1):164–73.
10. Mehta C, Mehta D, Shwayder T. Asymptomatic bands on an infant's extremity. Pediatr Dermatol. 2018;35(1):139–40.
11. Bernal E, Oeltjen JC. Constriction ring syndrome. J Craniofac Surg. 2009;20(4):1018–20.
12. Hung NN. Congenital constriction ring in children: sine plasty combined with removal of fibrous groove and fasciotomy. J Child Orthop. 2012;6(3):189–97.
13. Chen H. Atlas of genetic diagnosis and counseling. New York: Springer; 2012. p. 87–98.
14. Weinzweig N, Barr A. Radial, ulnar, and median nerve palsies caused by a congenital constriction band of the arm: single-stage correction. Plast Reconstr Surg. 1994;94(6):872–6.

Part III
Birth Trauma

Chapter 21
Birth Fractures

Michelle L. Sagan and Angielyn San Juan

Background

Musculoskeletal injuries sustained during birth are relatively uncommon and comprise <1% of live births [1]. Though rare, these injuries are important to recognize as the infant may present with non-specific signs or symptoms. The parents of newborns often feel overwhelmed and require guidance in helping care for the patient's injured extremity until fracture union. The most common injuries sustained during birth are clavicle fractures, followed by fractures of the humeral and femoral shaft, and physeal injuries. Improvements in obstetric care and prenatal diagnosis have decreased the overall incidence of perinatal trauma; however, it is important to recognize that despite this, these injuries still occur [2].

Epidemiology/Pathophysiology

In full-term infants, mechanical factors are a common cause of birth trauma [3]. In the absence of metabolic bone disease, multiple predisposing factors to injury have been identified and include vaginal delivery, primigravid mother, prolonged labor, use of instruments for delivery, infant weight > 4000 g, increasing gestational age,

M. L. Sagan (✉)
Division of Pediatric Orthopaedic Surgery and Sports Medicine, Ann and Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA
e-mail: msagan@luriechildrens.org

A. S. Juan
Department of Orthopaedics, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA

Northshore University Health System, Skokie, IL, USA
e-mail: asanjuan@northshore.org

J. F. Sarwark, R. L. Carl (eds.), *Orthopaedics for the Newborn and Young Child*,
https://doi.org/10.1007/978-3-031-11136-5_21

and shoulder dystocia [4]. Though the incidence of injury is higher in vaginal births than in breech births, fractures of long bones have been described in cesarean deliveries due to the use of forceful maneuvers [5].

The most common musculoskeletal injuries related to birth are clavicle fractures, with an overall incidence of 0.2–0.5% of births [6]. The incidence of clavicle fractures increases in patients with associated shoulder dystocia and concomitant brachial plexus injuries, with rates reported as high as 25% [7]. Of all the trauma sustained in the perinatal period, clavicle fractures comprise 90% of these injuries. The mechanism of injury often occurs after shoulder dystocia when during parturition, the infant's head is delivered but the anterior shoulder is impacted against the maternal pubis preventing further descent of the infant [7]. Multiple maneuvers have been described to help disimpact the shoulder, including suprapubic pressure, delivering the posterior shoulder with traction of the forearm, and rotation of the infant to enable delivery of the anterior shoulder. If these maneuvers are unsuccessful, intentional cleidotomy may be required. Fracture of the clavicle results from direct, compressive force of the maternal pubic symphysis on the infant's shoulder or the mechanical force exerted on the infant's extremity with the use of these maneuvers [8]. Though obstetric manipulation of the infant plays a role in contributing to these injuries, significant predisposing risk factors of clavicle fracture in the setting of shoulder dystocia have been identified and they include induction of labor and macrosomia (infant weight > 4000 grams) [6] (Figs. 21.1 and 21.2).

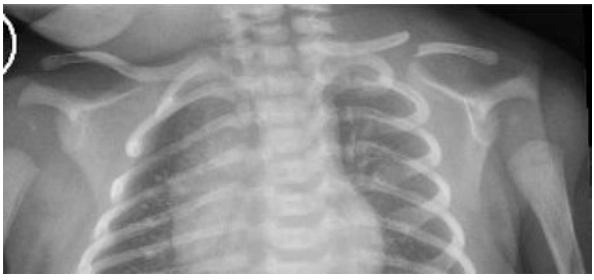


Fig. 21.1 A newborn with left clavicle fracture

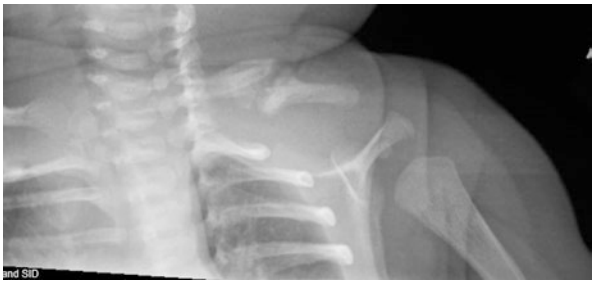


Fig. 21.2 The same newborn 4 weeks later with a large amount of callus surrounding the clavicle fracture

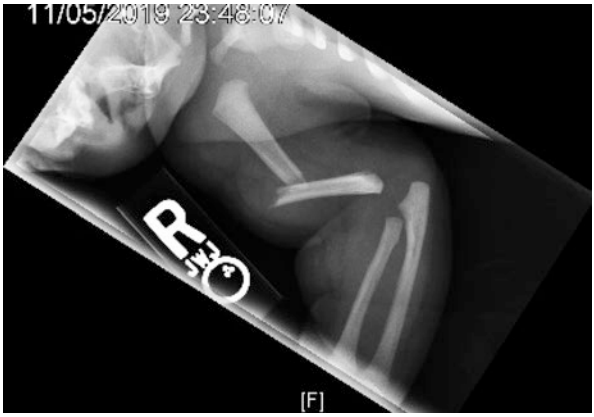


Fig. 21.3 Newborn with a right humerus birth fracture

Less commonly, fractures of the humeral shaft occur in about 1–2 per 10,000 live births [9]. The lower incidence of these injuries can be attributed to the greater amount of force that is required to fracture a long bone [10]. Fractures sustained in the humeral diaphysis occur as a result of excessive traction or rotational forces applied to the neonate's arm. This can occur in both vaginal and cesarean deliveries, though several studies have indicated a higher incidence of long bone fractures in cesarean deliveries for breech presentation (Figs. 21.3 and 21.4).

Diaphyseal fractures of the femur are extremely rare and have an incidence of 0.13 injuries per 1000 births [1]. Predisposing factors include twin gestation, breech presentation, and fetal osteoporosis. Similar to humeral shaft injuries, femur fractures occur when a considerable amount of traction and/or a rotational force is applied to the extremity during difficult deliveries. These injuries are more commonly sustained during delivery in cesarean sections, though have been also described to occur in vaginal births (Figs. 21.5 and 21.6).

Physeal injuries during birth are very rare injuries and have been described only in small case series and case reports [11]. The injury can occur at both the proximal and distal humeral physis where the relatively weak physis is susceptible to injury with rotational and shear forces. Given its relatively rare incidence and its difficulty with diagnosis both clinically and radiographically, these injuries are often missed. Specifically, distal humeral epiphyseal separation is rare, occurring in 1 out of 35,000 births and can be missed or misinterpreted as an elbow dislocation [12]. Though incredibly uncommon, it is important to recognize these entities as potential injuries so that an appropriate work-up can be performed and to initiate subsequent intervention (Figs. 21.7, 21.8, and 21.9).

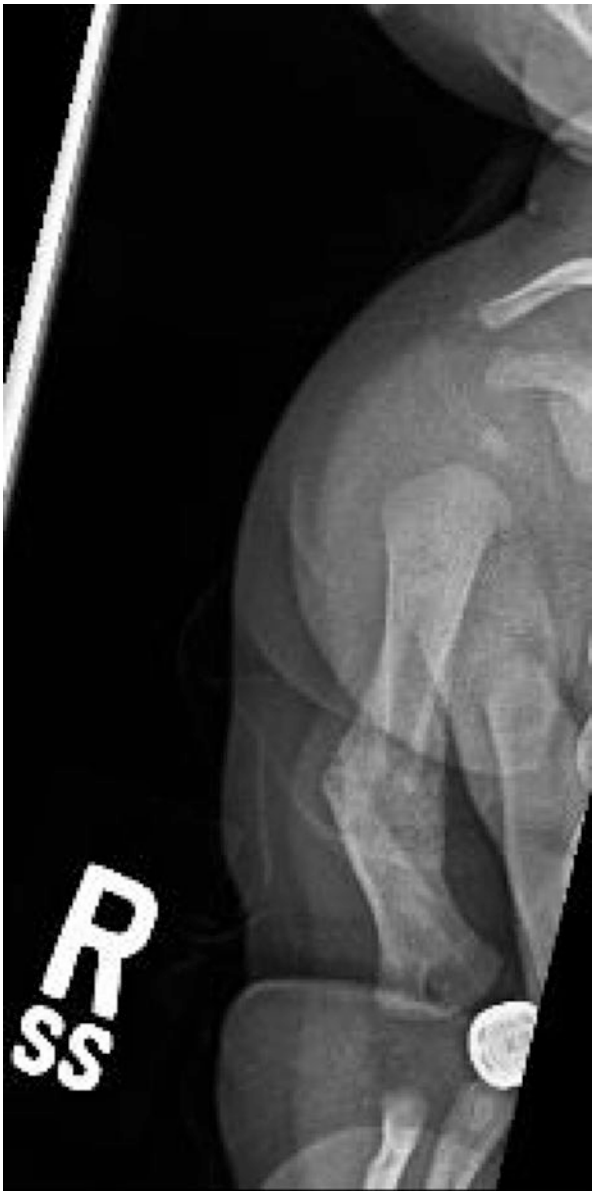


Fig. 21.4 Same newborn 2 months later with dramatic healing and remodeling of the humerus fracture

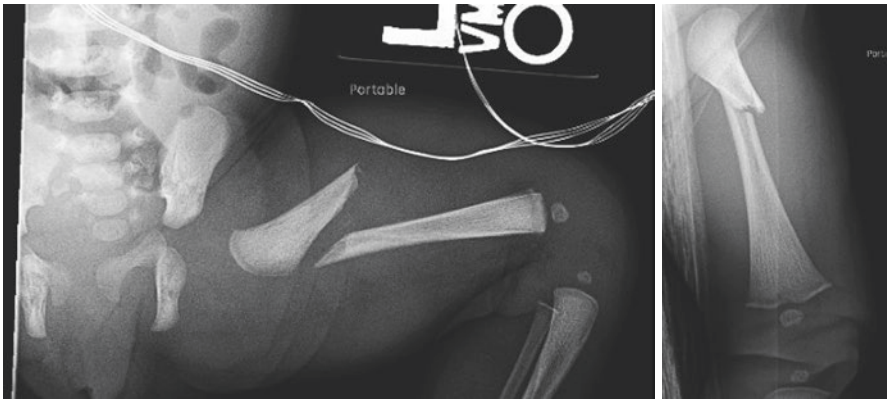


Fig. 21.5 Lateral and AP radiographs of a newborn with a femoral shaft fracture

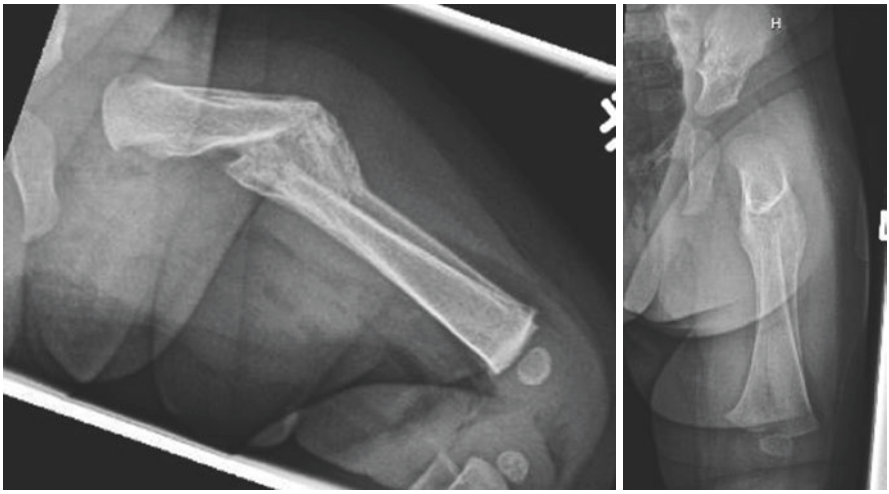


Fig. 21.6 Lateral and AP radiographs of the same newborn 8 weeks lateral with dramatic healing and remodeling of the femoral shaft fracture

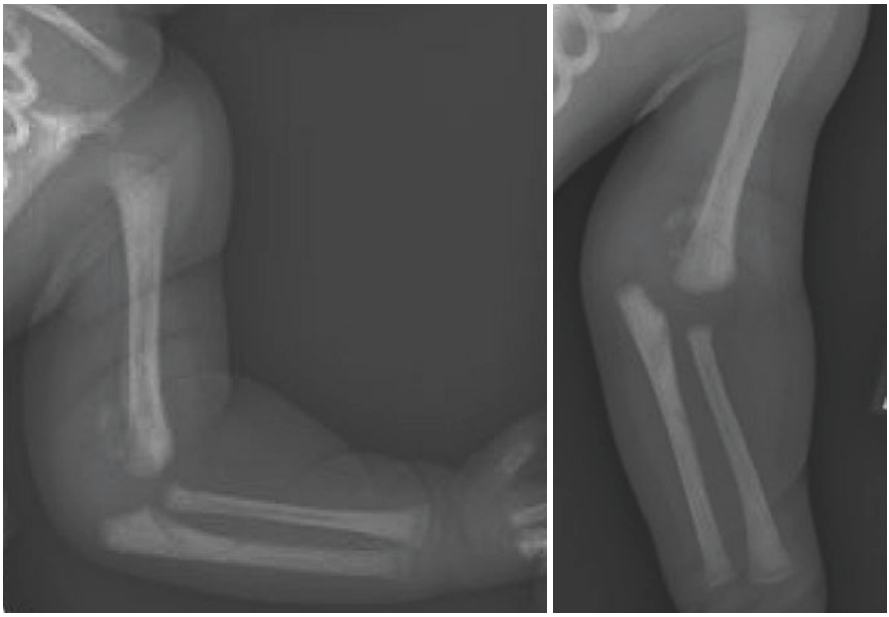


Fig. 21.7 2-week-old newborn with delayed diagnosis of a transphyseal birth fracture of the distal humerus. Transphyseal fracture, as opposed to an elbow dislocation, was confirmed by a trained musculoskeletal radiologist via ultrasound

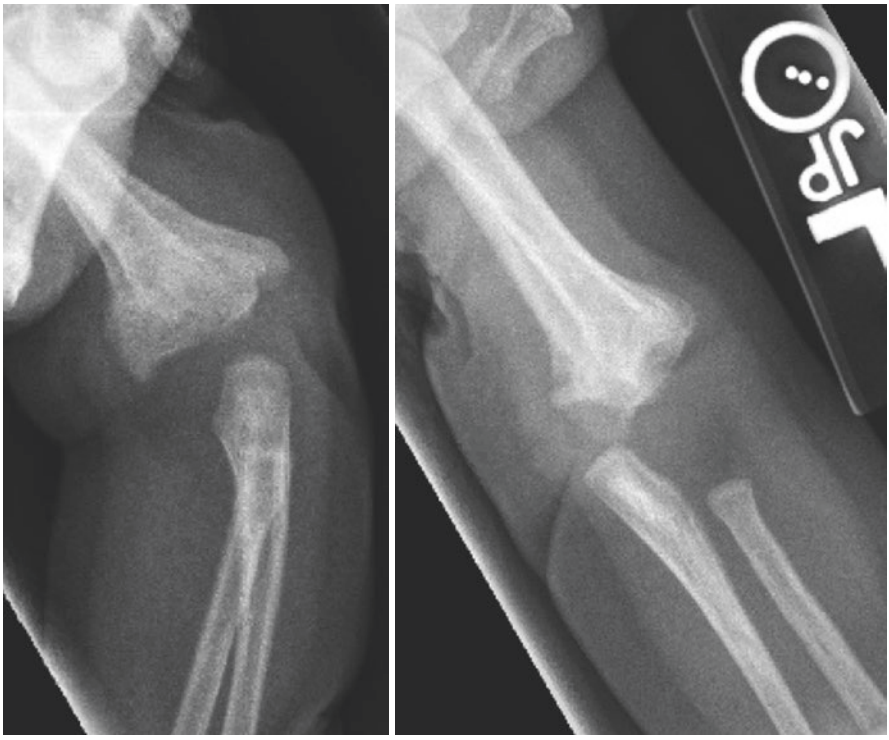


Fig. 21.8 Same infant with intermediate healing with continued deformity

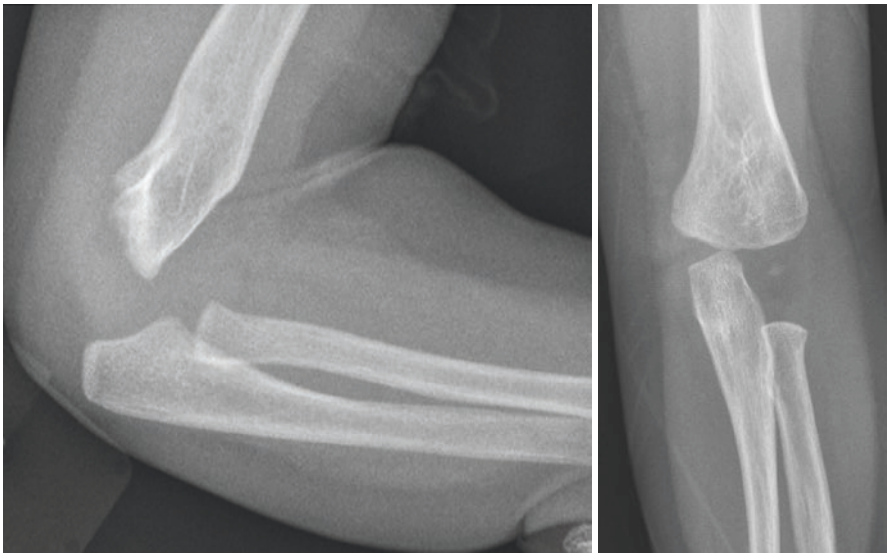


Fig. 21.9 2 years follow-up with near complete remodeling

Common Clinical Presentation: History and Physical

Physical examination of the neonate is challenging, and clinical findings that typically correlate with a fracture are not obvious. Due to this, these injuries are often missed at the time of birth, and the delay in diagnosis can be disconcerting for the parents and may cause prolonged discomfort for the infant. If an obvious injury during the time of delivery is recognized, oftentimes the obstetrician may feel or hear an audible pop or crack. This clues the clinician into closely evaluating that involved extremity and ordering imaging studies that would help correlate with the suspected diagnosis. In injuries detected days after birth, findings associated with fracture include swelling, erythema, and tenderness of the injured limb. The infant may be irritable or inconsolable. Delayed detection may also be complicated by the need to rule out postpartum nonaccidental trauma.

Patients with clavicle fractures will often have associated swelling, pain, and palpable crepitation. The injury may be diagnosed at birth, with one study demonstrating fracture recognition in 47% of cases [13], the other half of cases may be recognized days after delivery. The infant may present with decreased Moro reflex. In addition, a newborn with a clavicle fracture may present similarly to, or concurrent with, a brachial plexopathy. With upper trunk C5 and C6 nerve root injury (Erb's palsy) being the most common injury pattern, the patient will have an internally rotated arm with the wrist and fingers held in flexion [14].

Long bone fractures of the humeral or femoral diaphysis will present with swelling, deformity, and tenderness at the fracture site. Infants with humeral shaft fractures may have pseudoparalysis of the upper limb, as well as shoulder swelling and restricted passive range of motion [9].

Epiphyseal injuries have subtle physical examination findings and, depending on the physis involved, could be undetected for days or weeks after birth. With epiphyseal separation of the proximal humerus, infants can present with pseudoparalysis, swelling of the shoulder, and restricted active and passive range of motion [11]. Similarly, infants with epiphyseal separation of the distal humerus and proximal femur have limited range of motion and soft tissue swelling at the elbow and hip, respectively.

Treatment/Management

Treatment of these birth injuries is largely non-operative. Clavicle fractures are treated with symptomatic care and watchful waiting. The patient is followed both clinically and radiographically for fracture union. Humeral shaft fractures can be initially managed with temporary long arm posterior mold splints and have been described in the setting of bilateral injuries [15]. A majority of these fractures are treated with immobilization of the arm through swaddling, pinning the infant's sleeve to its clothing, or with the use of an elastic bandage. Humeral shaft fractures

have tremendous healing and remodeling potential and are successfully managed with this non-operative modality.

Diaphyseal femur fractures are also treated with immobilization through the use of Pavlik harness application, through the use of a posterior mold splint, or with fracture bracing. Clinical and radiographic union is evident at 4–6 weeks. Due to the great remodeling potential of this fracture pattern, the infant typically does not have any restriction in motion post-treatment [16].

Physeal separations require reduction of the epiphysis on the metaphysis. This is done through a closed versus open means and requires fixation of the reduced separation with K wire fixation. After confirmation of union, the K wires are subsequently removed [17]. When delayed diagnosis occurs, the risk of iatrogenic physeal arrest is high with any manipulation or reduction maneuvers. In these cases, the fracture is typically allowed to complete healing and remodeling without any attempts at correcting alignment. If appropriate remodeling does not correct the deformity, corrective surgery can be performed at a later date.

Natural History: Primary and Secondary Prevention

Identifying risk factors for difficult delivery can help the obstetrician prepare. These include:

- Macrosomia
- Prolonged second stage of labor
- Induction of labor
- Use of instruments

References

1. Morris S, Cassidy N, Stephens M, McCormack D, McManus F. Birth-associated femoral fractures: incidence and outcome. J Pediatr Orthop. 2002;22(1):27–30.
2. Perlow JH, Wigton T, Hart J, Strassner HT, Nageotte MP, Wolk BM. Birth trauma a five-year review of incidence and associated perinatal factors. J Reprod Med. 1996;41(10):754–60.
3. Chaturvedi A, Chaturvedi A, Stanescu AL, Blickman JG, Meyers SP. Mechanical birth-related trauma to the neonate: an imaging perspective. Insights Imaging. 2018;9(1):103–18. https://doi.org/10.1007/s13244-017-0586-x.
4. Levine MG, Holroyde J, Woods JR, Siddiqi TA, Scott M, Miodovnik M. Birth trauma: incidence and predisposing factors. Obstet Gynecol. 1984;63(6):792–5.
5. Kaya B, Daglar K, Kirbas A, Tüten A. Case report humerus diaphysis fracture in a newborn during vaginal breech delivery. Case Rep Obstetr Gynecol. 2015;2015:1–3. https://doi.org/10.1155/2015/489108.
6. Karahanoglu E, Kasapoglu T, Ozdemirci S, Fadıloglu E, Akyol A, Demirdag E, et al. Risk factors for clavicle fracture concurrent with brachial plexus injury. Arch Gynecol Obstetr. 2016;293(4):783–7. https://doi.org/10.1007/s00404-015-3917-5.

7. Politi S, D'Emidio L, Cignini P, Gioriandino M, Gioriandino C. Shoulder dystocia: an evidence-based approach. J Prenat Med. 2010;4(3):35–42.
8. Beall MH, Ross MG. Clavicle fracture in labor: risk factors and associated morbidities. J Perinatol. 2001;21(8):513–5. https://doi.org/10.1038/sj.jp.7210594.
9. Husain SN, King EC, Young JL, Sarwark JF. Remodeling of birth fractures of the humeral diaphysis. J Pediatr Orthop. 2008;28(1):10–3.
10. Al-Habdan I. Birth-related fractures of long bones. Indian J Pediatr. 2003;70:959–60. https://doi.org/10.1007/BF02723819.
11. El-adl WA, Elgohary HSA, Elshennawy MM. Epiphyseal separation of the proximal humerus after birth trauma. Eur J Orthop Surg Traumatol. 2014;24(6):863–7. https://doi.org/10.1007/s00590-013-1276-0.
12. Tharakan SJ, Lee RJ, White AM, Lawrence JTR. Distal humeral epiphyseal separation in a newborn. Orthopedics. 2016;39(4):e764–7. https://doi.org/10.3928/01477447-20160503-01.
13. Ahn ES, Jung MS, Lee YK, Ko SY, Shin SM, Hahn MH. Neonatal clavicular fracture: recent 10 year study. Pediatr Int. 2015;57(1):60–3. https://doi.org/10.1111/ped.12497.
14. Chater M, Camfield P, Camfield C. Erb's palsy—who is to blame and what will happen? Paediatr Child Health. 2004;9(8):556–60. https://doi.org/10.1093/pch/9.8.556.
15. Canpolat FE, Köse A, Yurdakök M. Bilateral humerus fracture in a neonate after cesarean delivery. Arch Gynecol Obstetr. 2009;281(5):967–9. https://doi.org/10.1007/s00404-009-1256-0.
16. Stannard JP, Christensen KP, Wilkins KE. Femur fractures in infants: a new therapeutic approach. J Pediatr Orthop. 2006;15:461–6. https://doi.org/10.1097/01241398-199507000-00010.
17. Jacobsen S, Hansson G, Nathorst-Westfelt J. Traumatic separation of the distal epiphysis of the humerus sustained at birth. J Bone Joint Surg Br. 2009;91-B(6):797–801. https://doi.org/10.1302/0301-620X.91B6.22140.

Chapter 22
Pediatric Brachial Plexus Palsy

Muhammad Y. Mutawakkil and Erik C. B. King

Brief Overview of Condition

The brachial plexus is a network of nerves that traverses from the cervical spinal cord through the shoulder region and into the arm. A brachial plexus injury or palsy results when the nerve roots and/or nerves of the brachial plexus are stretched, torn, or compressed. A loss of movement or weakness of the arm may occur if these nerves are damaged. Sensory impairment also occurs. Brachial plexus injury that is diagnosed during the perinatal period is commonly referred to as pediatric brachial plexus palsy (PBPP), brachial plexus birth palsy (BPBP), or neonatal brachial plexus palsy (NBPP). PBPP is typically noticed at the time of birth when the newborn has decrease spontaneous motion of the affected arm.

Due to varying clinical manifestation of brachial plexus injuries, management can range from arm immobilization and physical therapy to microsurgical reconstruction of affected nerve roots to restore function. Orthopedic surgery on the muscle, tendon, joints, and bones is also performed to address orthopedic impairment, but usually is performed after the age of 18 months.

M. Y. Mutawakkil
Department of Orthopaedic Surgery, Northwestern University Feinberg School of Medicine, Chicago, IL, USA
e-mail: muhammad.mutawakkil@northwestern.edu

E. C. B. King (✉)
Department of Orthopaedic Surgery, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA
e-mail: eking@luriechildrens.org

J. F. Sarwark, R. L. Carl (eds.), *Orthopaedics for the Newborn and Young Child*,
https://doi.org/10.1007/978-3-031-11136-5_22

Background Including Epidemiology and Pathophysiology

The brachial plexus is an elaborate network of peripheral nerves that arise from the C5-T1 ventral spinal nerve roots. Variant contributions from C4 and T2 may occur. If C4 contributes, the brachial plexus is classified as prefixed, and if T2 contributes, the brachial plexus is considered postfixed [1]. The C5-T1 nerve roots give rise to trunks, divisions, cords, and terminal branches (Fig. 22.1). The C5 and C6 nerve roots of the brachial plexus merge to become the upper trunk. The C7 nerve root continues alone to become the middle trunk. The C8 and T1 nerve roots merge to form the lower trunk. Each of the three trunks divides into anterior and posterior divisions. All the posterior divisions converge to make the posterior cord, which then gives rise to the radial and axillary nerve. The anterior division of the superior trunk and medial trunk merge to form the lateral cord, which gives rise to the musculocutaneous nerve and contribution to the median nerve. The anterior division of the lower trunk continues to form the medial cord, which gives rise to the ulnar nerve and the remaining contributions to the median nerve. Besides these major

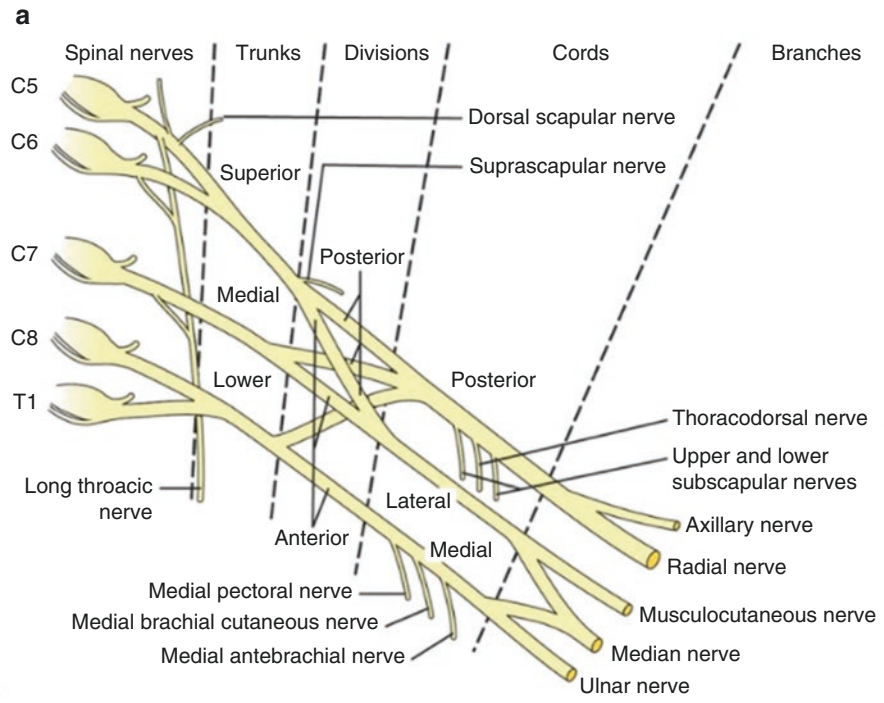


Fig. 22.1 (**a**) Normal brachial plexus. (**b**) Brachial plexus spectrum of injury: neuropraxia, axonotmesis, neurotmesis, and avulsion. Figures reprinted from Green's Operative Hand Surgery, Seventh Edition, Wolfe S, Pederson W, Kozin S, Cohen M, Chap. 40: Pediatric Brachial Plexus Palsy, Cornwall R, Waters PM, pp. 1391–1424, © 2017, with permission from Elsevier [2]

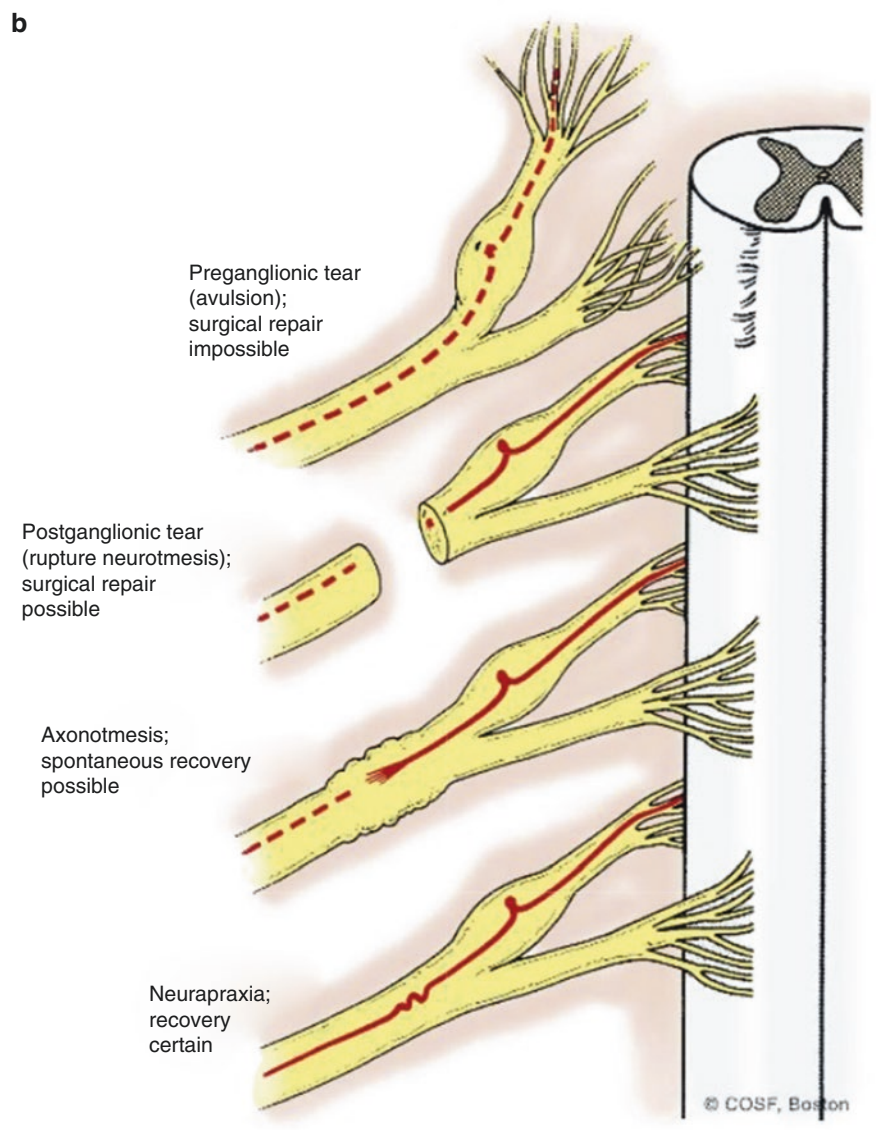


Fig. 22.1 (continued)

nerves, several smaller nerves and branches arise from different sections of the brachial plexus. Collectively, the nerves of the brachial plexus provide all the motor and sensory innervation to the upper extremity.

The incidence and severity of brachial plexus palsy have been minimized by modern obstetric care. Despite these improvements, the occurrence of brachial plexus palsy has not been eliminated. The incidence of brachial plexus palsy is

approximately 1.51 per 1000 live births [3]. Perinatal risk for PBPP factors includes large fetal size (macrosomia), maternal diabetes, multiparous pregnancies, prolonged delivery, breech delivery, shoulder dystocia, vacuum assisted delivery, forceps assisted delivery, and difficult deliveries. BPBP is associated with shoulder dystocia in about 50% of cases.

The mechanism of birth-related brachial plexus injury is stretch across one or more nerve components of the brachial plexus resulting in varying degree of nerve dysfunction. Extrinsic and intrinsic causes have been proposed. Considerable medical and legal debate has surrounded the etiology of the stretch. Obstetrical techniques are often cited as being responsible for the injury because lateral traction is sometimes applied to the head of the infant to facilitate delivery of the shoulder past the pubic symphysis. However, published reports have suggested alternative etiologies.

Brachial plexus injuries are described as neuropraxia, axonotmesis, neurotmesis, or avulsion (Fig. 22.1) [4]. In neuropraxia, the stretch on the brachial plexus causes disruption of neuronal function, but the neuronal structure remains intact. Recovery is expected to be complete. In axonotmesis, there is disruption of axons and myelin sheath, but the endoneurial tube is intact. Good recovery will occur without intervention. In neurotmesis, there is complete disruption of all endoneurial and perineurial structures. Surgical repair is required to restore neural continuity. Avulsion is the most devastating form of injury. This type of injury is a preganglionic tear and as a result of the injury location, avulsions cannot be directly repaired surgically.

Clinical Presentation: History and Physical

Factors that contribute to the difficult passage of fetus through the birth canal are associated with brachial plexus injuries. These factors include gestational diabetes, macrosomia, shoulder dystocia, prolonged labor, instrumented delivery, breech delivery, and fetal distress resulting in hypotonia. Although rare, non-traumatic causes of neonatal brachial plexus palsy have been described. The differential diagnoses for non-traumatic etiologies include infection (varicella syndrome, humeral, or vertebral osteomyelitis), compression (exostosis of the first rib, tumors, hemangiomas), and familial congenital hypoplastic brachial plexus palsy [5].

The most notable finding of PBPP in the newborn physical examination is decreased movement of all or part of the affected upper extremity. In addition to decreased spontaneous movement, infantile reflexes, such of the Moro or tonic neck reflex, may be absent. When the lower plexus is involved, grasp reflex may also be absent. Careful serial examinations will enable the examiner to determine the pattern of muscular impairment and thus enable conclusions about the locus, or loci, of injury within the brachial plexus. Sympathetic nerves can also be affected if the T1 nerve root is involved. Injury to T1 will result in Horner's syndrome: ptosis, miosis, and anhidrosis. In approximately 5% upper plexus lesions, the nerve roots forming the phrenic nerve or the phrenic nerve itself can also be injured, causing weakness

and elevation of the ipsilateral hemidiaphragm [6]. Clavicle, humerus, or other long bones are seen in 10% of patients. Even in the absence of PBPP, a clavicle fracture or humerus fracture may simulate brachial plexus palsy, a temporary condition, referred to as "pseudo-paralysis."

Narakas has categorized the clinical continuum of brachial plexus palsy into four groups based on the nerve roots injured and the resulting clinical manifestation [7]. In group I (Erb-Duchenne type or Erb's palsy), the upper nerve roots C5-C6 are affected. This manifests as weakness of the shoulder abductors, external rotators, elbow flexors, and wrist extensors. As a result, the newborn will exhibit the classic "waiter's tip" position: shoulder adduction, shoulder internal rotation, elbow extension, and wrist flexion (Fig. 22.2). Group I is the most common form of PBPP. In group II (extended Erb's palsy), the lesion is localized to C5, C6, and C7. Weakness in elbow extension and shoulder adduction is added to those deficits of group I. Group III (total plexus palsy) is a global palsy with lesion affecting C6 through T1. Newborns present with flaccid paralysis of the upper extremity. Clawing of the hand (intrinsic minus position) and persistent forearm supination may also be noted (Fig. 22.3).

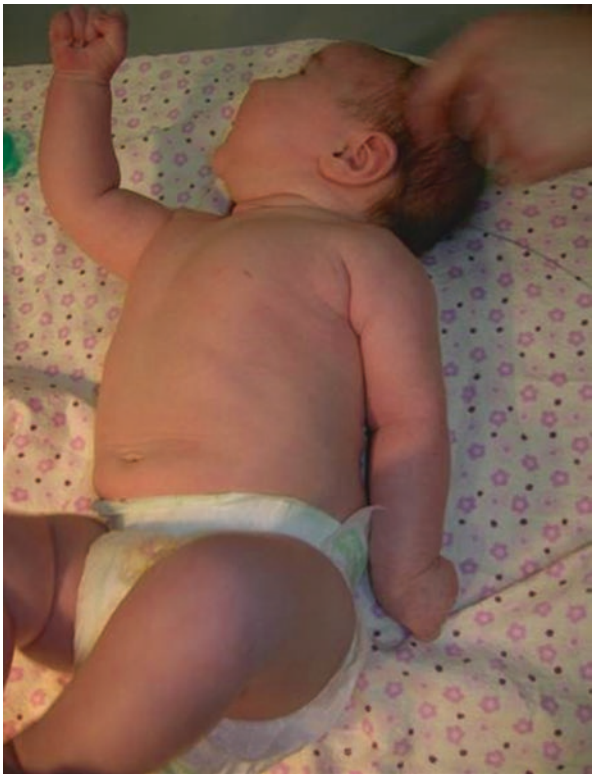


Fig. 22.2 C5–6 brachial plexus palsy (Erb-Duchenne). Shoulder adduction, shoulder internal rotation, elbow extension, and wrist flexion

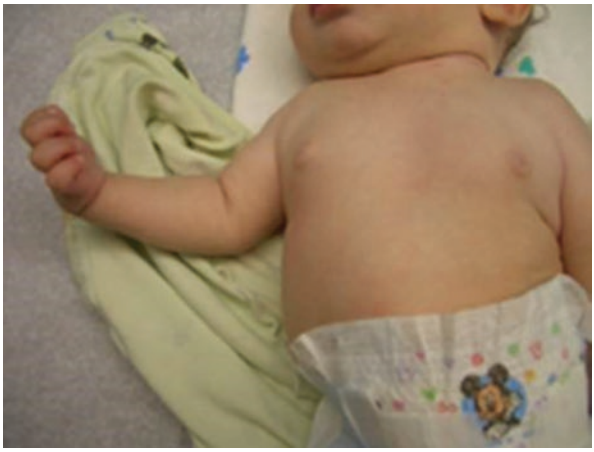


Fig. 22.3 Total plexus palsy flaccid paralysis, clawing of the hand and persistent forearm supination

Group IV (total plexus palsy with a Horner) is total plexus palsy plus Horner's syndrome. This classification scheme does not include isolated involvement of the lower trunk (C8-T1). Isolated involvement of the lower trunk is rare.

Evaluation

As mentioned previously, clinical examination is usually sufficient to diagnose brachial plexus injuries. Any decrease in the degree of spontaneous arm movement, reflexes, or position should warrant a closer examination of the upper extremities. Careful inspection of muscle groups in the upper arm will lead to the anatomic pattern of brachial plexus injury, but the definitive pattern will be refined with serial examinations over time. The child should also be evaluated for ipsilateral ptosis or miosis to rule out concomitant Horner's syndrome. Finally, the clavicle and humerus should be examined evidence of trauma: deformity, ecchymosis, crepitus, and pain. The role for imaging in the immediate postnatal period is limited to radiographs to diagnose clavicle or humerus fractures.

Management

The goal of management of PBPP is to maximize functional outcome. Initial treatment during the first week of life consists of protecting the affected upper limb by swaddling of the arm or pinning the child's shirt sleeve to keep the arm close to the body. Because muscle imbalance and soft tissue contractures can develop rapidly, physiotherapy (physical therapy and occupational therapy) should be initiated as soon as the newborn can tolerate passive range of motion and stretching. If

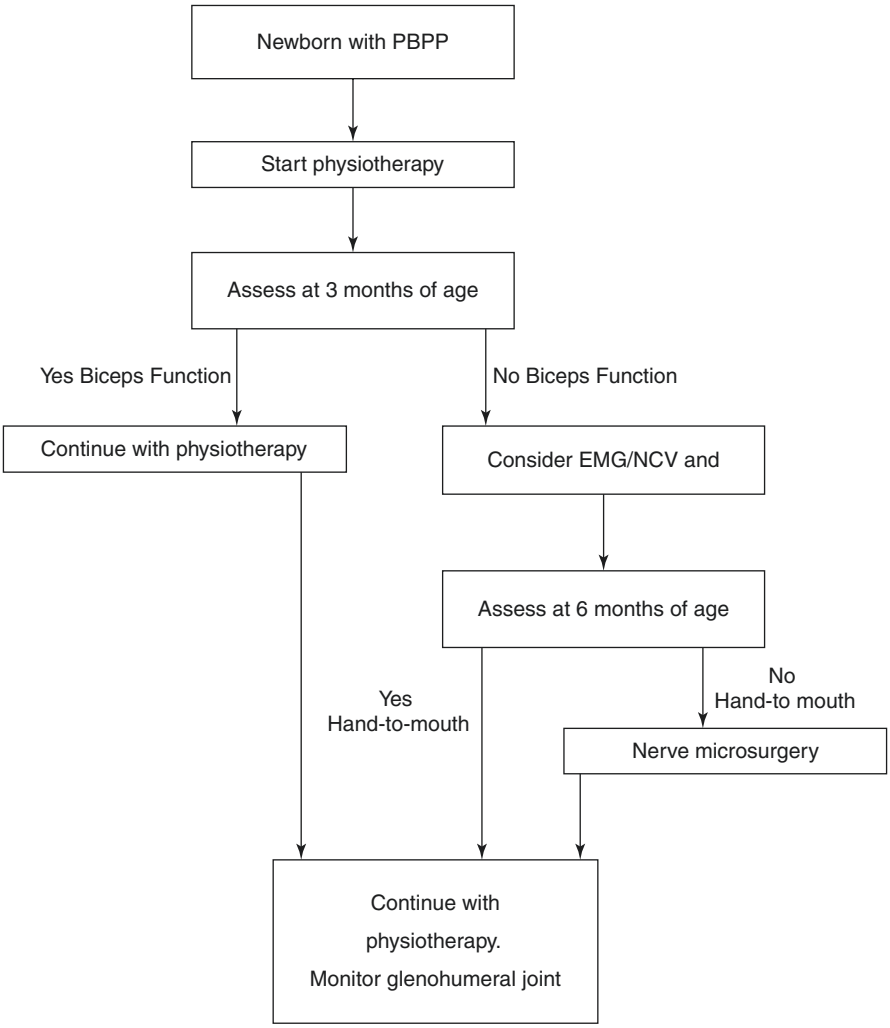


Fig. 22.4 Treatment algorithm for pediatric brachial plexus palsy (PBPP)

available, children with brachial plexus palsy should be referred to a multidisciplinary team consisting of physiatrists, neurologic surgeons, orthopedic surgeons, physical therapists, occupational therapists, and orthotists. A typical management algorithm for a patient with brachial plexus palsy is shown in Fig. 22.4.

Careful physical examination should be repeated frequently. Spontaneous motor recovery may be subtle at first. Any early improvement in neurologic function is a positive predictor of further neurologic recovery, and thus can be reassuring to parents. If biceps function returns within the first 6 weeks of life, ultimate normal recovery is expected [8]. If biceps recovery does not begin by 3 months of age, ultimate spontaneous recovery will be less than complete. The presence of pain and/

or loss of shoulder range of motion may indicate the development of shoulder joint subluxation or dislocation. Radiographic or ultrasound evaluation of the shoulder is warranted if decreased passive external rotation of the shoulder is noted. Patients should also be screened for associated conditions including torticollis and early speech delay [9, 10].

Most cases of PBPP are transient and will resolve naturally by 3–4 months of age. If significant deficits persist after this time, microsurgery to repair or reconstruct the injured nerves may be considered. Electromyogram (EMG) and somatosensory evoked potential (SSEP) studies may be used to confirm the absence of sufficient neurologic recovery. In some cases, these studies can localize the neurologic lesion. However, some surgeons have found these studies to be unreliable, and so these surgeons prefer to rely exclusively on physical examination for surgical decision-making [11].

Indications for nerve reconstruction include nerve root avulsions and lack of recovery of biceps antigravity function by 6 months of age. However, the timing, technique, and role of surgery remain controversial. Several sources recommend that if there is no return of biceps strength against gravity to perform hand to mouth gestures ("cookie test") by the age of 6 months, then microsurgery is indicated. Conversely, if there is biceps antigravity function by 6 months of age, microsurgery is not beneficial and should not be performed. The majority of patients fall into this category. This latter group of patients is better served by ongoing physiotherapy and consideration for musculoskeletal surgery for residual deficits after 6–12 months of age.

Nerve microsurgery options include neurolysis, neuroma resection, nerve grafting, and/or nerve transfers. In nerve grafting, autogenous nerve graft, such as sural nerve, is placed as a conduit between the two ends of the affected nerve after the neuroma is resected. Nerve transfers typically involved sacrificing the nerves of muscles with redundant function in order to restore vital motions to the arm. Normal arm function is not expected after microsurgery, and families are advised that there will be residual neurological deficits (Fig. 22.5). Donor nerves include intercostal and spinal accessory nerves.

PBPP patients who do not have complete neurologic recovery will experience weakness and muscular imbalance, and hence functional impairment. In addition, muscular imbalance over time will lead to secondary bone and joint deformity. Commonly in C5-C6 involved patients, shoulder adduction and internal rotation contractures cause progressive glenohumeral deformity. The amount of skeletal deformity is best assessed with a three-dimensional imaging: MRI or CT.

In order to address functional impairment and glenohumeral deformity, patients with incomplete motor recovery may benefit from musculoskeletal surgical procedures. These procedures are typically performed after 18 months of age. Indications for shoulder surgery include glenohumeral dislocation, persistent internal rotation contracture, limitation in external rotation and above shoulder function, and/or glenohumeral deformity [8]. Shoulder surgical procedures include botulinum toxin A injection followed by casting, subscapularis muscle tendon lengthening, open surgical joint reduction, arthroscopic joint reduction, muscle tendon releases and

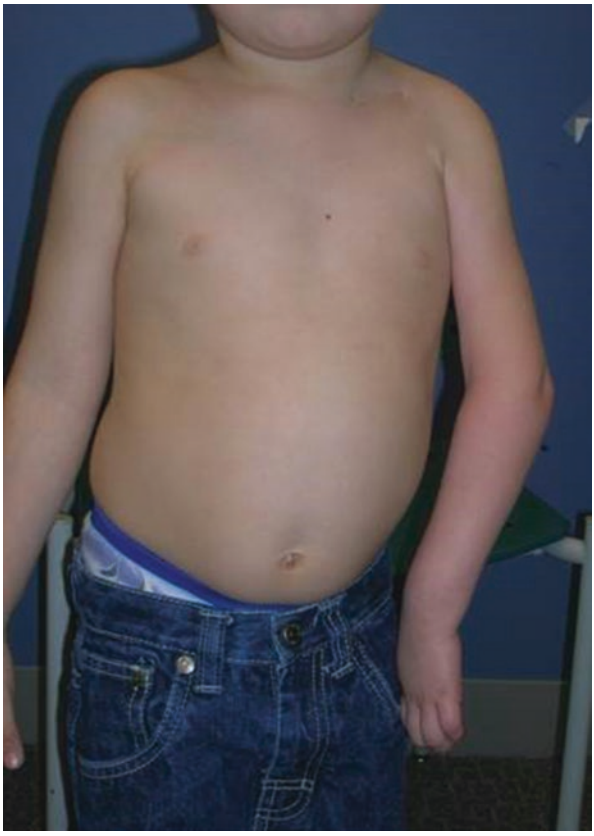


Fig. 22.5 Global plexus palsy in a child after microsurgery. Note healed surgical incisions on left anterior shoulder and residual neurological deficits

transfers, and humeral osteotomy. In addition, other surgical procedures on the elbow, forearm, and hand are performed to address specific deficits.

Clinical Pearls

- The risks factors for PBPP are large fetal size (macrosomia), maternal diabetes, multiparous pregnancies, prolonged delivery, breech delivery, shoulder dystocia, vacuum assisted delivery, forceps assisted delivery, and difficult deliveries.
- Improved obstetrical techniques have decreased the incidence of PBPP.
- Injury of C5–6 (Erb-Duchenne) is the most common pattern.
- Physiotherapy should be initiated as soon as possible.
- Most cases of PBPP are transient and will resolve naturally by 3–4 months of age.
- If biceps recovery does not begin by 3 months of age, ultimate spontaneous recovery will be less than complete.

- Nerve microsurgery is considered for those children who do not regain biceps antigravity function by 6 months of age.
- Orthopedic musculoskeletal surgery is usually performed after 18 months of age.

References

1. Al-Qattan MM, Clarke HM, Curtis CG. Klumpke's birth palsy. Does it really exist? J Hand Surg (Br). 1995;20:19–23.
2. Cornwall R, Waters PM. Chapter 40: Pediatric brachial plexus palsy. In: Wolfe S, Pederson W, Kozin S, Cohen M, editors. Green's operative hand surgery. 7th ed. New York: Elsevier; 2017. p. 1391–424.
3. Foad SL, Mehlman CT, Foad MB, Lippert WC. Prognosis following neonatal brachial plexus palsy: an evidence-based review. J Children's Orthopaedics. 2009;3(6):459–63.
4. Abzug JM, Kozin SH. Evaluation and management of brachial plexus birth palsy. Orthop Clin North Am. 2014;45:225–32.
5. Tierney TS, Tierney BJ, Rosenberg AE, Krishnamoorthy KS, Butler WE. Infantile myofibromatosis: a nontraumatic cause of neonatal brachial plexus palsy. Pediatr Neurol. 2008;39(4):276–8.
6. Ho C. Chapter 15: Disorders of the upper extremity. In: Tachdjian's pediatric orthopaedics: from the Texas Scottish rite hospital for children. 5th ed. Dallas: Elsevier; 2014. p. 461–70.
7. Narakas AO. Obstetrical brachial plexus injuries. In: Lamb DW, editor. The paralysed hand, vol. 2. Edinburgh: Churchill Livingstone; 1987. p. 116–35.
8. Hale HB, Bae DS, Waters PM. Current concepts in the management of brachial plexus birth palsy. J Hand Surg Am. 2010;35(2):322–31.
9. Hervey-Jumper SL, Justice D, Vanaman MM, Nelson VS, Yang LJ. Torticollis associated with neonatal brachial plexus palsy. Pediatr Neurol. 2011;45(5):305–10.
10. Chang KW, Yang LJ, Driver L, Nelson VS. High prevalence of early language delay exists among toddlers with neonatal brachial plexus palsy. Pediatr Neurol. 2014;51(3):384–9.
11. Blaauw G, Slooff AC. Transfer of pectoral nerves to the musculocutaneous nerve in obstetric upper brachial plexus palsy. Neurosurgery. 2003;53(2):338–41. discussion 41.

Suggested Readings/Additional Resources

Buterbaugh KL, Shah AS. The natural history and management of brachial plexus birth palsy. Curr Rev Musculoskel Med. 2016;9(4):418–26.

Foad SL, Mehlman CT, Ying J. The epidemiology of neonatal brachial plexus palsy in the United States. J Bone Joint Surg Am. 2008;90:1258.

Hoeksma AF, ter Steeg AM, Nelissen RG, van Ouwerkerk WJ, Lankhorst GJ, de Jong BA. Neurological recovery in obstetric brachial plexus injuries: an historical cohort study. Dev Med Child Neurol. 2004;46:76–83.

Pitt M, Vredeveld JW. The role of electromyography in the management of the brachial plexus palsy of the newborn. Clin Neurophysiol. 2005;116:1756–61.

Pondaag W, Malessy MJ. The evidence for nerve repair in obstetric brachial plexus palsy revisited. Biomed Res Int. 2014;2014:434619.

Pondaag W, Malessy MJ, van Dijk JG, Thomeer RT. Natural history of obstetric brachial plexus palsy: a systematic review. Dev Med Child Neurol. 2004;46(2):138–44.

Seddon SH. Lesions of individual nerves: upper limb. In (eds): Surgical disorders of the peripheral nerves. London: Churchill Livingstone; 1949.
Shenaq SM, Bullocks JM, Dhillon G, Lee RT, Laurent JP. Management of infant brachial plexus injuries. Clin Plast Surg. 2005;32:79–98.
Smith BW, Daunter AK, Yang LJ, Wilson TJ. An update on the management of neonatal brachial plexus palsy-replacing old paradigms: a review. JAMA Pediatr. 2018;172(6):585–91.
Squitieri L, Larson BP, Chang KW-C, Yang LJ-S, Chung KC. Understanding long-term outcomes and patient expectations among adolescents with neonatal brachial plexus palsy: a qualitative and quantitative study. J Hand Surg. 2013;38(12):2387–2397.e2.
Wilson TJ, Chang KWC, Yang LJS. Prediction algorithm for surgical intervention in neonatal brachial plexus palsy. Neurosurgery. 2018;82(3):335–42.
Yang LJ. Neonatal brachial plexus palsy—management and prognostic factors. Semin Perinatol. 2014;38(4):222–34.

Part IV
Systemic Conditions and Syndromes with Orthopaedic Manifestations

Chapter 23
Achondroplasia

Haley E. Smith

Brief Overview of Condition

Achondroplasia is the most common non-lethal skeletal dysplasia with an incidence of 1 in 26,000 [1, 2]. It is estimated that 250,000 people are affected by the condition worldwide [3]. The condition is characterized by a prenatal onset of rhizomelic dwarfism. In most cases, achondroplasia is associated with normal intellectual development, relatively good health, and normal lifespan. However, abnormal bone development may result in numerous orthopedic, neurologic, otolaryngologic, and social complications [4].

Background Including Epidemiology and Pathophysiology

Achondroplasia is caused by a G380 point mutation of the gene encoding fibroblast growth factor receptor-3 (FGFR-3) on the short arm of chromosome 4. FGFR-3 is a regulator of linear bone growth. The receptor is expressed in all pre-bone cartilage and inhibits chondrocyte proliferation and differentiation. The G380 mutation seen in almost all cases of achondroplasia results in a glycine-to-arginine substitution in the transmembrane domain of the tyrosine-coupled receptor. This is a gain of function mutation of the FGFR-3 receptor, which increases the inhibition of chondrocyte proliferation in the proliferative zone of the physis [5]. Ultimately, this results in the underdevelopment of bones formed by endochondral ossification.

Achondroplasia is inherited as an autosomal dominant trait with 100% penetrance. However, approximately 90% of cases occur from a de novo mutation. Paternal age over 36 years has been associated with increased incidence of

H. E. Smith (✉)
Department of Orthopedics, Northwestern University, Chicago, IL, USA
e-mail: haley.smith@northwestern.edu

J. F. Sarwark, R. L. Carl (eds.), *Orthopaedics for the Newborn and Young Child*,
https://doi.org/10.1007/978-3-031-11136-5_23

achondroplasia. Most patients with achondroplasia are heterozygous. Homozygous cases of achondroplasia are typically fatal in the neonatal period [5, 6].

Clinical Presentation: History and Physical

The most notable clinical feature in children with achondroplasia is short stature with disproportionately shortened proximal limb segment—a pattern known as rhizomelic dwarfism. At birth, length is preserved in achondroplasia; however short limbs, a long trunk and narrow thorax are typically noted. The disproportionate short stature becomes progressively more evident with final adult height averaging 125 cm for males and 120 cm for females [2].

Abnormal endochondral ossification leads to underdeveloped facial bones and orocraniofacial characteristics that are identifiable at birth. The characteristics typical for achondroplastic babies include frontal bossing, maxillary hypoplasia, prominent mandibles, a flattened nasal bridge, and relative macrocephaly [7].

With regard to the extremities, patients have trident hands with an increased separation and an inability to oppose the middle and ring fingers (Fig. 23.1). The digits are all of equal length, short, and broad. Flexion contractures may occur at both the hip and elbow, with the elbow contracture possibly resulting from radial

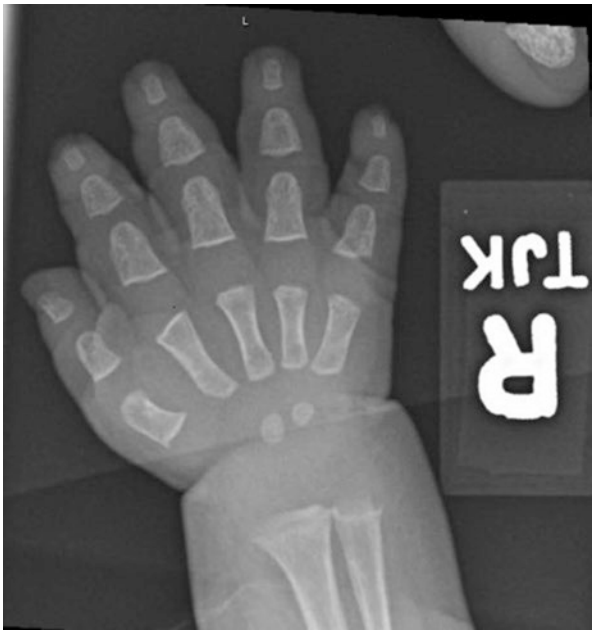


Fig. 23.1 The trident hand is a classic clinical finding in achondroplasia. The fingers are short, and the divergence of the third and fourth fingers gives hands the three pronged "trident" appearance

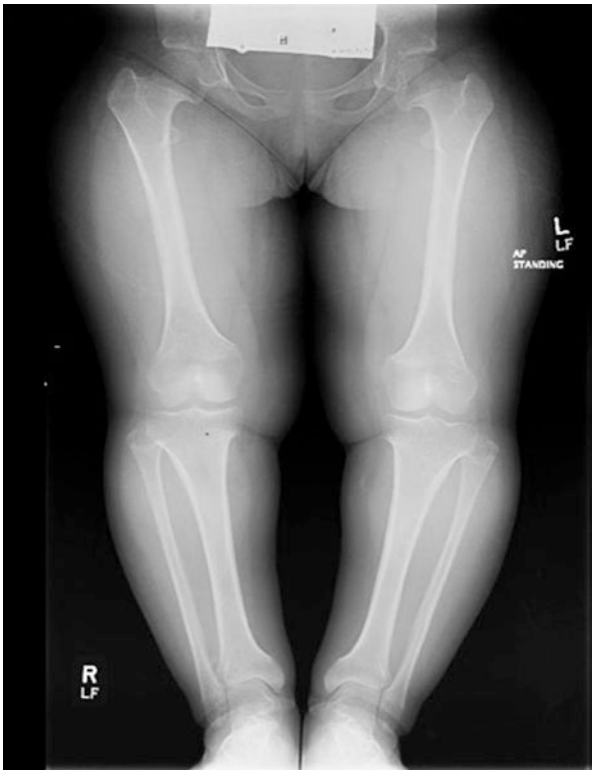


Fig. 23.2 The full length standing lower extremity films demonstrate classic rhizomelic shortening of the long bones with genu varum

head dislocation. While contractures occur at the more proximal joints, the more distal joints are hypermobile [8]. Genu varum is also a key feature of achondroplasia; the etiology of the malalignment is likely multifactorial but may be related to relative fibular overgrowth [9] (Fig. 23.2).

Achondroplastic patients have mild generalized hypotonia at birth resulting in delayed motor milestones. Thoracolumbar kyphosis is common in infancy, but most cases correct spontaneously as children begin to walk and muscle tone improves. The spinal deformity commonly transitions into excessive lumbar lordosis [10].

Other clinical features include a high incidence of childhood obesity with a protuberant abdomen and prominent buttocks, which are exaggerated by the lumbar lordosis. Motor development typically normalizes by age 3. Children may continue to have a waddling gait due to lower extremity and pelvic deformity. Intellectual development is on par with peers, but numerous studies have demonstrated a high incidence of psychosocial issues in patients with non-lethal skeletal dysplasias [8].

Evaluation

Achondroplasia is suspected prenatally when the fetus has disproportionately small limbs on ultrasound evaluation (<3rd percentile). In most cases, obvious limb shortening in achondroplasia only becomes apparent early in the third trimester. Other clinical features that may be apparent on ultrasound include frontal bossing, bowing of the femurs, short fingers, small chest, and polyhydramnios. Accurate diagnosis of skeletal dysplasias is difficult, and only 30% of cases are correctly diagnosed based on prenatal ultrasound [11]. Occasionally, an early diagnosis of achondroplasia can be confirmed by detecting the FGFR3 mutation with chorionic villus sampling at 11–13 weeks or amniocentesis after 15 weeks [8].

Most cases of achondroplasia are confirmed postnatally by clinical genetic consultation, clinical features, and radiographic findings. The tubular bones are shortened in a rhizomelic pattern with flared metaphyses. Because the width of the long bones results from intramembranous periosteal ossification, the bones are of normal diameter. The physis may appear to be "U" or "V" shaped and appears to hug the unaffected epiphyses. This feature is most clinically apparent in the distal femur (Fig. 23.3). The tibia and femur may also be bowed [12].

Spinal radiographs demonstrate key diagnostic findings of achondroplasia. The spinal canal normally widens in the lumbar spine, however in patient with achondroplasia there is narrowing of the interpedicular distance from L1 to L5, which is best viewed on the anteroposterior view of the lumbar spine [8]. Lateral radiographs of the spine are also useful in diagnosis, with findings including short and broad pedicles and scalloped posterior vertebral bodies [6, 13].

In achondroplasia, the pelvis appears broad and flat with square ilia, and the sciatic notches are narrowed with sharp ischial spines. Disturbances of endochondral ossification at the triradiate cartilage result in a flattened and horizontal acetabulum. A shortened femoral neck in relation to a normal sized greater trochanter may give the appearance of coxa vara; however, true varus is not present [12] (Fig. 23.4).

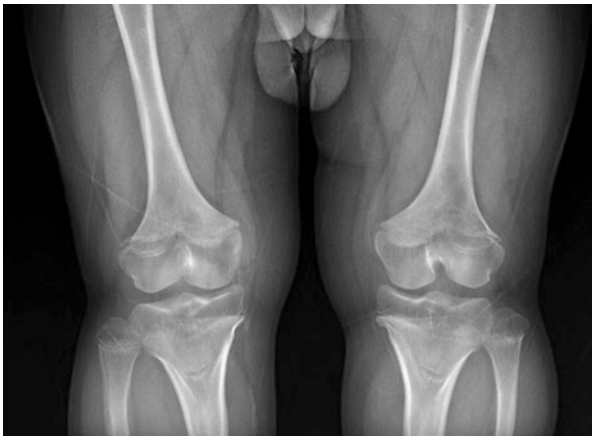


Fig. 23.3 AP radiograph of bilateral knees demonstrates the flared metaphyses, which are most prominently seen in the distal femur

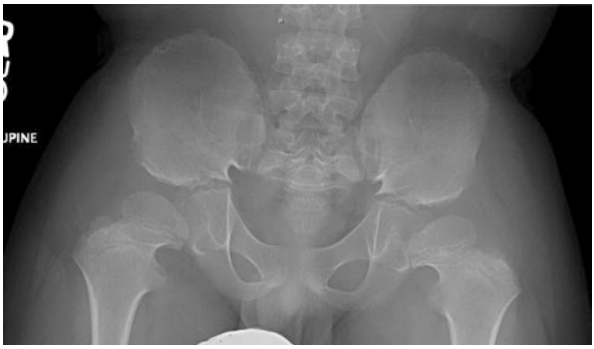


Fig. 23.4 The AP radiograph of the pelvis shows the squared or "mickey-mouse" appearing iliac wings, short sacroiliac notches, and a horizontal acetabular roof

Other radiographic abnormalities associated with achondroplasia include short, wide, and cupped phalanges, underdeveloped facial bones, a small foramen magnum, and a shortened skull base [8].

Management

Foramen magnum stenosis (FMS) is an early spinal manifestation to develop and typically presents within the first 2 years of life. Like the other features of achondroplasia, FMS is the result of abnormal endochondral ossification of the occipital bone. This condition poses a significant medical risk to achondroplastic patients. In general, patients with achondroplasia have a normal life expectancy, but there is an increased likelihood of sudden death in patients under the age of 4 (up to 7.5%) attributed to the compression of vital structures contained in the foramen magnum and upper cervical spine. The most common presenting symptom is respiratory difficulties or excessive snoring due to central sleep apnea. Other symptoms of chronic brainstem compression include lower cranial nerve dysfunction, dysphagia, hyperreflexia, hypotonia, clonus, and severe developmental delay. Recent studies have demonstrated that infants with significant cord compression may be asymptomatic on clinical exam and have normal polysomnography. It is therefore recommended that all infants with achondroplasia are screened with magnetic resonance imaging (MRI) and polysomnography by 6 months of age. Imaging should be repeated at 2 years of age if the initial imaging is within normal limits [4, 14].

Relatively few infants require treatment for FMS. The treatment involves foramen magnum decompression, suboccipital craniectomy, and upper cervical laminectomy. Surgical decompression is warranted in all infants presenting with concerning clinical symptoms and findings of stenosis and cord indentation on MRI. However, because the severity of clinical symptoms does not always correlate with the findings on imaging, there continues to be controversy regarding the need for and timing of surgical intervention [15].

Thoracolumbar Kyphosis

Thoracolumbar kyphosis is another spinal manifestation of achondroplasia that develops during infancy, with a reported incidence of up to 94% in patients under the age of 12 months [16]. The kyphosis results from the relatively large head in combination with generalized hypotonia and trunk weakness. The curvature is typically most prominent from T10 to L4 and corrects when the patient is placed in the prone position [10]. Most cases spontaneously improve as the muscle tone and strength improve as the patient begins to walk. Approximately one-third of patients will have persistent thoracolumbar kyphosis. Persistent motor developmental delay (as compared to motor development of other achondroplastic patients), apical vertebral translation and apical vertebral wedging are associated with higher rates of persistent kyphosis. Untreated persistent thoracolumbar kyphosis can result in deformity progression, severe hip flexion contractures, and worsening spinal stenosis [16].

In mild kyphosis, Pauli et al. recommend that parents are counseled to use firm-backed seating and prohibit sitting up at more than 60° to avoid the progression of deformity until the child can independently ambulate [17]. Early bracing was traditionally initiated if a fixed curve >30° developed or if radiographs demonstrated anterior wedging or translation of the vertebral apex. However, there are concerns with bracing due to an increased risk of falls and detrimental effects on pulmonary function. Patients with persistent curves between 20 and 40° should be monitored for deformity progression and neurologic compromise.

Surgical intervention with a posterior spinal fusion and laminectomy are performed for patients with curves >40° or in patients with neurological deficits [16]. Fusion is also recommended for all patients with kyphosis undergoing a laminectomy for stenosis [6]. Unless the curve or neurologic deficits are rapidly progressing, the surgery is usually delayed until at least 4 years of age to allow for the use of instrumentation [8]. The surgical correction should be limited to the degree of correction attainable on a hyperextension lateral radiograph while the patient is awake [10]. Current surgical options include posterior, anterior, and combined approaches. Arthrodesis may be performed in a single- or multi-staged fashion [18]. Because of the narrowed spinal canal, wires, laminar hooks, or other instrumentation that enters the spinal canal are contraindicated and pedicles screws are favored for fusion. Safe instrumentation requires knowledge of the achondroplastic pedicle morphology. The average pedicle length is approximately 10 mm shorter than in patients without achondroplasia. The sagittal pedicle diameter is slightly smaller, with a normal transverse diameter. The pedicles are directed cranially at all levels. These morphologic differences must be considered in screw length and diameter selection as well as in the trajectory of hardware placement [8, 13].

Spinal Stenosis

The abnormal endochondral ossification of the vertebrae results in morphological abnormalities increasing the risk for spinal stenosis. The vertebral bodies are shortened, and the pedicles are shortened and thickened. In addition, the intervertebral disks and ligamentum flavum are hyperplastic. In comparison to healthy patients, these abnormalities reduce the diameter of the spinal canal by approximately 40% [8].

Symptomatic spinal stenosis typically presents in the second or third decades of life, but it has been reported in patients as early as 18 months [10]. The reported incidence of spinal stenosis ranges from 37 to 89% [2]. Patients present with neurogenic claudication symptoms including lower back pain, numbness and tingling, leg pain, and weakness of the lower extremities. These symptoms are relieved by bending-over, sitting down or squatting—maneuvers which all increase the size of the canal and reduce cord impingement [8].

Mild stenosis may be managed conservatively with activity modification and anti-inflammatory medications. Surgical indications include severe claudication with the inability to walk more than two city-blocks, neurologic symptoms at rest, and bowel and bladder dysfunction. Surgical management of spinal in stenosis with achondroplasia is significantly more challenging. Inadequate decompression is a common error in surgical management. The laminectomy should extend three levels above the level of the most severe stenosis and at least down to S2. Lateral stenosis is common in achondroplasia; therefore, the laminectomy should be widened, and nerve root recesses on both sides should be explored. A posterior spinal fusion with pedicle screw instrumentation should be done concurrently to prevent progressive kyphosis in skeletally immature patients undergoing a laminectomy of five or greater levels. Posterior decompression can be done alone without a concurrent fusion in skeletally mature patients [3, 8].

Lower Extremity Angular Deformities

Angular deformities of the lower extremities are present in most achondroplastic children, with genu varum and tibia vara being more common than valgus deformities. The cause of genu varum is likely multifactorial; lateral collateral ligament laxity and fibular overgrowth are probable factors (Fig. 23.5). Patients with genu varum may be asymptomatic or they may present with knee pain, neurologic symptoms, knee instability, or waddling gait [9]. Despite the angular deformity, progression to degenerative arthritic changes is rare in the achondroplastic population.

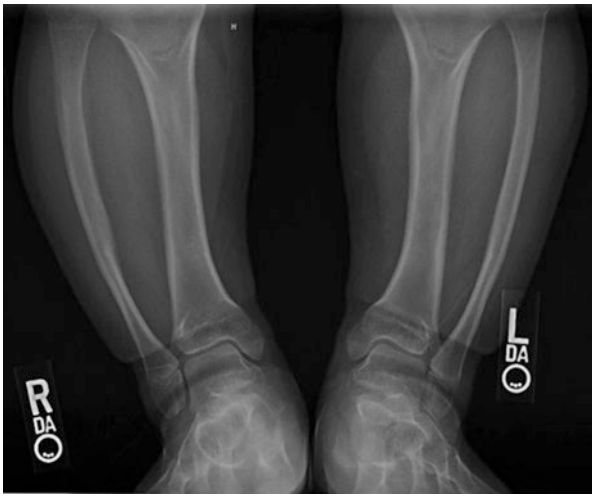


Fig. 23.5 Fibular overgrowth and bowing are potential causes of lower limb angular deformity

Initially bracing was used to control ligamentous laxity and correct malalignment; however, studies and clinical practice have demonstrated minimal success with this treatment [10]. Additionally, bracing frequently causes peroneal nerve palsies in achondroplastic patients [18]. Surgical decisions should be delayed until at least 3 years of age. At this time, the indications for surgery are not clearly defined. The natural history of the deformity has not been closely studied or linked to long-term degenerative changes. However, most clinicians will opt to proceed with surgical management when the patient is experiencing persistent pain attributed to the malalignment or when the deformity is severe enough to cause a fibular thrust or results in gaping at the knee on standing or ambulation [8, 9]. Most commonly, a tibial osteotomy with or without femoral osteotomy with fixation can correct the deformity. Tibial torsion should be concurrently addressed. Due to the ligamentous laxity in the achondroplastic knee, the mechanical axis should be restored through precise bony alignment, rather than kinematically through the knee joint by stressing the medial collateral ligament [6].

Short Stature

Short stature is the most notable feature of achondroplasia. By adulthood, patients are six to seven standard deviations below the average height of unaffected individuals. Significant daily impairment can result from short stature including difficulties with hygiene, engaging in hobbies or sports, conducting business at a countertop level, and driving a car. Studies have also demonstrated self-esteem and emotional difficulties linked to short stature. Short stature has been addressed by the use of growth hormone and rare elective limb lengthening [19].

Limb Lengthening

Surgical limb lengthening usually requires multiple operations occurring between 7 and 13 years of age over months of time. The average length gain is 9.8 cm in the tibia and 8.4 cm in the femur. The Ilizarov external fixator and distraction osteogenesis are most commonly used for elective limb lengthening. Lengthening of greater than 20% of initial bone length results in more frequent complications, including malunion, malalignment, infection, fractures, and joint stiffness [19]. Spinal stenosis may also be worsened by lower limb lengthening. Surgical lengthening of the lower extremities is a time-consuming process and requires an average of 3 years of rehabilitation. Humeral lengthening may also be attempted to improve upper extremity functions such as combing hair, putting on shoes and socks, and extending reaching. Humeral lengthening results in a gain of 8–12 cm in arm length. Upper extremity lengthening has a much lower rate of complications and requires an average of 9 months of treatment time [10]. Further studies are needed on the functional gains following limb lengthening so that the benefit of increased limb length can be appropriately considered against the significant complication rate.

Growth Hormone

Although patients with achondroplasia are not growth hormone (GH) deficient, GH treatment may improve linear growth. Initial studies demonstrated the greatest effect on growth velocity in the first year of treatment. Additionally, younger patients saw the most significant results. Further research has demonstrated average increase in height of 6–8 cm without an increase in trunk-limb disproportion. Growth hormone treatment may worsen spinal stenosis in achondroplasia. Furthermore, growth hormone treatment in the general pediatric population has been linked to increased risks of diabetes and malignancy. The benefit of several centimeters of height gain should be weighed against the potential risks before initiating treatment [8, 20].

Other Medical Complications

Otolaryngeal problems are extremely common in achondroplasia patients. 75% of the patients with achondroplasia have recurrent otitis media before they are 2 years old, and approximately 50% of patients will require ear tube placement [1]. Recurrent otitis media may result in hearing difficulties and speech delay. Due to facial hypoplasia, adenoid and tonsil hypertrophy can result in obstructive sleep apnea.

Hydrocephalus is frequently suspected in achondroplastic patients due to their large head circumference. Clinically significant hydrocephalus occurs on rare occasion in achondroplasia. Ventricular-peroneal shunting is indicated only for rapid progression of head circumference or for signs of increased intracranial pressure [15, 20].

Patients with achondroplasia have a greater incidence of obesity. Specific achondroplastic weight-for-height and weight-for age curves should be used to determine ideal body weight [8].

The social and emotional difficulties of dwarfism should not be overlooked. Quality of life studies demonstrate that patients with achondroplasia were found to have significantly lower income, less education, were less likely to married, and had lower self-esteem than their healthy peers [4, 20].

Clinical Vignettes/Clinical Pearls

1. Patients with achondroplasia are best cared for by a multidisciplinary team with expertise in skeletal dysplasia. Anticipatory care should be directed at identifying and preventing the development of serious sequelae [21].
2. Every infant with achondroplasia should be screened for foramen magnum stenosis and resulting in cervicomedullary compression. The American Academy of Pediatrics recommends screening with a thorough neurologic history, physical, neuroimaging (CT or MRI), and polysomnography [21].
3. Achondroplastics are at risk for spinal canal stenosis, which may result in cauda equine or nerve root compression. Surveillance and early intervention is key.
4. The benefits of gaining centimeters of height must be weighed against the medical and psychosocial risks when considering limb lengthening or growth hormone treatment.

References

1. Hunter AG, Bankier A, Rogers JG, Sillence D, Scott CI Jr. Medical complications of achondroplasia: a multicentre patient review. J Med Genet. 1998;35(9):705–12.
2. Baujat G, Legeai-Mallet L, Finidori G, Cormier-Daire V, Le Merrer M. Achondroplasia. Best Pract Res Clin Rheumatol. 2008;22(1):3–18.
3. Horton WA, Hall JG, Hecht JT. Achondroplasia. Lancet. 2007;370(9582):162–72.
4. Ceroni JRM, Soares DCQ, Testai LC, Kawahira RSH, Yamamoto GL, Sugayama SMM, et al. Natural history of 39 patients with Achondroplasia. Clinics (Sao Paulo). 2018;73:e324.
5. Laederich MB, Horton WA. FGFR3 targeting strategies for achondroplasia. Expert Rev Mol Med. 2012;14:e11.
6. Herring J. Tachdjian's pediatric orthopaedics: from the Texas Scottish rite hospital for children. 5th ed. Philadelphia: Saunders/Elsevier Health; 2013.
7. Pineau M, Farrow E, Nicot R, Ferri J. Achondroplasia: orocraniofacial features and orthodontic-surgical management guidelines proposal. J Craniofac Surg. 2018;29(8):2186–91.

8. Shirley ED, Ain MC. Achondroplasia: manifestations and treatment. J Am Acad Orthop Surg. 2009;17(4):231–41.
9. Ain MC, Shirley ED, Pirouzmanesh A, Skolasky RL, Leet AI. Genu varum in achondroplasia. J Pediatr Orthop. 2006;26(3):375–9.
10. Lovell WW, Weinstein SL, Flynn JM. Lovell and Winter's pediatric orthopaedics. 7th ed. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2014.
11. Schramm T, Gloning KP, Minderer S, Daumer-Haas C, Hortnagel K, Nerlich A, et al. Prenatal sonographic diagnosis of skeletal dysplasias. Ultrasound Obstet Gynecol. 2009;34(2):160–70.
12. Bailey JA 2nd. Orthopaedic aspects of achondroplasia. J Bone Joint Surg Am. 1970;52(7):1285–301.
13. Srikumaran U, Woodard EJ, Leet AI, Rigamonti D, Sponseller PD, Ain MC. Pedicle and spinal canal parameters of the lower thoracic and lumbar vertebrae in the achondroplast population. Spine (Phila Pa 1976). 2007;32(22):2423–31.
14. Sanders VR, Sheldon SH, Charrow J. Cervical spinal cord compression in infants with achondroplasia: should neuroimaging be routine? Genet Med. 2018.
15. White KK, Bompadre V, Goldberg MJ, Bober MB, Campbell JW, Cho TJ, et al. Best practices in the evaluation and treatment of foramen magnum stenosis in achondroplasia during infancy. Am J Med Genet A. 2016;170A(1):42–51.
16. Margalit A, McKean G, Lawing C, Galey S, Ain MC. Walking out of the curve: thoracolumbar kyphosis in achondroplasia. J Pediatr Orthop. 2018;38(10):491–7.
17. Pauli RM, Breed A, Horton VK, Glinski LP, Reiser CA. Prevention of fixed, angular kyphosis in achondroplasia. J Pediatr Orthop. 1997;17(6):726–33.
18. Ain MC, Shirley ED. Spinal fusion for kyphosis in achondroplasia. J Pediatr Orthop. 2004;24(5):541–5.
19. Kim SJ, Agashe MV, Song SH, Choi HJ, Lee H, Song HR. Comparison between upper and lower limb lengthening in patients with achondroplasia: a retrospective study. J Bone Joint Surg Br. 2012;94(1):128–33.
20. Trotter TL, Hall JG. American Academy of Pediatrics Committee on Genetics. Health supervision for children with achondroplasia. Pediatrics. 2005;116(3):771–83.
21. American Academy of Pediatrics. www.aap.org.

Chapter 24
Other Osteochondrodysplasias

Rebecca L. Carl

Diastrophic Dysplasia

Brief Overview

Diastrophic dysplasia (DTD) is a condition that results in abnormal bone and cartilage development. Individuals with DTD exhibit short stature, joint contractures, dislocations of large joints, and clubfoot deformity. Additionally, children with DTD typically develop progressive spine deformities including kyphosis and scoliosis [1]. Facial deformities may also be associated. Diastrophic dysplasia has autosomal recessive inheritance and results from mutations in the *SLC26A2* gene (also known as the *DTDST* gene) on chromosome 5q32 [2].

Epidemiology and Pathophysiology

In the United States, DTD affects about 1 in 100,000 newborns [3]. Finland has a much higher prevalence of DTD [1, 3–5]. Diastrophic dysplasia is inherited in an autosomal recessive pattern. Mutations in the solute carrier family 26 member 2 (*SLC26A2)* gene, also known as the diastrophic dysplasia transporter (*DTDST)* gene on chromosome 5 result in DTD [1, 2] The *SLC26A2* gene encodes a sulfate

R. L. Carl (✉)
Feinberg School of Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL, USA
e-mail: rcarl@luriechildrens.org

J. F. Sarwark, R. L. Carl (eds.), *Orthopaedics for the Newborn and Young Child*,
https://doi.org/10.1007/978-3-031-11136-5_24

transport protein. Chondrocytes are responsible for making sulfated proteoglycans. Mutations of the *SLC26A2* gene prevent proper sulfation of cartilage matrix proteoglycans [6].

Clinical Presentation

Children with DTD have short stature with rhizomelic (proximal limb) shortening. Clubfoot deformity is often present and can be difficult to treat. Metacarpal and phalangeal abnormalities, including an abducted position of the thumb ("hitchhiker's thumb") are also common in affected individuals. Children often develop a progressive scoliosis as early as the first few years of life. Kyphosis and atlantoaxial instability can also be associated with DTD. Contractures of the elbows, knees, and hips develop in many patients [1, 2]. Young children with DTD often exhibit gross motor delays related to their skeletal deformities [7].

Ear abnormalities including swelling of the pinnae and "cauliflower" ears are common [1]. Micrognathia, a small chest cavity, and/or cleft palate are present in some patients and can result in respiratory issues.

Evaluation

Rhizomelic shortening and thumb abnormalities may be visualized on prenatal ultrasound suggesting the diagnosis of DTD in the developing fetus.

In infants and children with DTD, radiographs of the spine are recommended to look for cervical abnormalities and developing scoliosis. Magnetic resonance imaging of the spine may be needed when there is suspicion of atlantoaxial instability.

When DTD is suspected clinically, skeletal survey radiographs can be helpful for identifying other skeletal deformities associated with DTD. Evaluation by a geneticist and molecular genetic testing for the *SLC26A2* can provide confirmation of a diastrophic dysplasia diagnosis [4].

Management

Orthopedic treatment is determined based on each individual's clinical phenotype and function. Affected children generally require physical therapy to address joint contractures and promote gross motor development.

The Ponseti method of casting and percutaneous Achilles tenotomy can be tried as the initial treatment for clubfoot deformity. In children with DTD, clubfoot may be difficult to manage, and additional surgical treatment may be required [3].

For children with progressive scoliosis, performing spinal fusion surgery when growth is complete or nearly complete is desirable. However, children with rapidly progressive scoliosis and those with signs of cervical spine instability may require earlier intervention [3].

Natural History and Prevention Strategies

Adults with DTD have marked short stature. Cognitive development is normal in individuals with DTD [5].

In children with DTD, scoliosis and joint contractures are typically progressive. For spine abnormalities, periodic surveillance with radiographs is crucial for determining when intervention is warranted.

Chondroectodermal Dysplasia (Ellis–van Creveld Syndrome)

Brief Overview

In 1940, Drs. Ellis and van Creveld described 3 individuals exhibiting a syndrome of abnormal teeth, thin/scarce hair, short limbs, polydactyly, distal phalangeal hypoplasia, and cardiomegaly [8] As more individuals with a similar phenotype were subsequently identified, physicians recognized an expanded list of clinical features as being part of Ellis–van Creveld syndrome (also known as chondroectodermal dysplasia) [1, 9, 10].

Ellis–van Creveld syndrome (EvC) has an autosomal recessive pattern of inheritance and results from mutations in the EVC or EVC2 genes on chromosome 4p16 [11].

Epidemiology and Pathophysiology

The incidence of EvC is estimated to be about 1 in 60,000 [12]. Ellis–van Creveld is inherited in an autosomal recessive pattern [9–11]. In 2000, Ruiz-Perez et al. discovered the EVC gene on chromosome 4p16 [9]. The same group subsequently identified a second gene, EVC2, on 4p16 [10]. Nonsense and frameshift mutations in these genes lead to Ellis–van Creveld syndrome. Proteins produced by the EVC and EVC2 genes are found at the base of osteoblast primary cilia [13]. The Indian hedgehog (Ihh) signaling protein controls growth plate development; primary cilia are involved in this signal pathway [14]. Disruption in normal EVC and EVC2 production leads to abnormalities of chondrocyte proliferation and growth [14].

Clinical Presentation

Children with Ellis–van Creveld syndrome (EvC) exhibit short limb, with the bones of the lower leg and forearms disproportionately affected. Hand abnormalities, including polydactyly, hypoplastic phalanges, carpal bone malformations, and dysplastic nails are common. Genu valgum and patellar dislocations are also frequently present [1, 11].

In their original description of EvC, Drs. Ellis and van Creveld noted that cardiomegaly was a feature of this condition [8]. Atrial septal defect is now recognized as the most common cardiac abnormality [11].

Characteristic facial features include a short philtrum and small, dysplastic teeth [1, 11].

Evaluation

Radiographic findings demonstrate that characteristic hand and limb abnormalities support a diagnosis of EvC. Proximal hypoplasia with the lateral tibial plateaus and abnormal iliac wing shape are also characteristic of this syndrome [1].

Genetics evaluation is recommended for individuals with clinical features of EvC.

Molecular analysis for mutations in the EVC and EVC2 genes is available for confirmatory testing [12].

Management

Surgical intervention is commonly needed for polydactyly.

The hand abnormalities associated with EvC may confer a higher risk of fine motor development delays. Occupational therapy should be considered for children with difficulty attaining fine motor milestones.

Echocardiogram screening and/or referral to pediatric cardiology should be considered given the high rates of atrial septal abnormalities in patients with EvC.

Natural History and Prevention Strategies

Children with EvC appear to have a high risk of growth hormone deficiency [15]. Referral to pediatric endocrinology is warranted for patients with signs of growth delay.

References

1. Jones KL, Crandall M, Del Campo M. Osteochondral dysplasias. In: Smith's recognizable patterns of human malformation. 7th ed. Philadelphia: Elsevier; 2013. p. 432–517.
2. Online Mendelian Inheritance in Man (OMIM), Diastrophic Dysplasia-222600. Johns Hopkins University, Baltimore, MD. https://www.omim.org/entry/222600. Accessed 4 May 2020.
3. Bonafe L, Mittaz-Crettol L, Ballhausen D, Superti-Furga A. Diastrophic dysplasia. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. . Seattle (WA): GeneReviews((R)); 1993.
4. Makitie O, Geiberger S, Horemuzova E, et al. SLC26A2 disease spectrum in Sweden—high frequency of recessive multiple epiphyseal dysplasia (rMED). Clin Genet. 2015;87(3):273–8.
5. Makitie O, Kaitila I. Growth in diastrophic dysplasia. J Pediatr. 1997;130(4):641–6.
6. Hastbacka J, de la Chapelle A, Mahtani MM, et al. The diastrophic dysplasia gene encodes a novel sulfate transporter: positional cloning by fine-structure linkage disequilibrium mapping. Cell. 1994;78(6):1073–87.
7. Crockett MM, Carten MF, Hurko O, Sponseller PD. Motor milestones in children with diastrophic dysplasia. J Pediatr Orthop. 2000;20(4):437–41.
8. Ellis RW, van Creveld S. A syndrome characterized by ectodermal dysplasia, polydactyly, chondro-dysplasia and congenital morbus cordis: report of three cases. Arch Dis Child. 1940;15(82):65–84.
9. Ruiz-Perez VL, Ide SE, Strom TM, et al. Mutations in a new gene in Ellis-van Creveld syndrome and Weyers acrodental dysostosis. Nat Genet. 2000;24(3):283–6.
10. Ruiz-Perez VL, Tompson SW, Blair HJ, et al. Mutations in two nonhomologous genes in a head-to-head configuration cause Ellis-van Creveld syndrome. Am J Hum Genet. 2003;72(3):728–32.
11. Online Mendelian Inheritance in Man (OMIM), Ellis-van Creveld-225500. Johns Hopkins University, Baltimore, MD. https://www.omim.org/entry/222600. Accessed 4 May 2020.
12. D'Asdia MC, Torrente I, Consoli F, et al. Novel and recurrent EVC and EVC2 mutations in Ellis-van Creveld syndrome and Weyers acrofacial dysostosis. Eur J Med Genet. 2013;56(2):80–7.
13. Valencia M, Lapunzina P, Lim D, et al. Widening the mutation spectrum of EVC and EVC2: ectopic expression of Weyer variants in NIH 3T3 fibroblasts disrupts Hedgehog signaling. Hum Mutat. 2009;30(12):1667–75.
14. Pacheco M, Valencia M, Caparros-Martin JA, Mulero F, Goodship JA, Ruiz-Perez VL. Evc works in chondrocytes and osteoblasts to regulate multiple aspects of growth plate development in the appendicular skeleton and cranial base. Bone. 2012;50(1):28–41.
15. Versteegh FG, Buma SA, Costin G, de Jong WC, Hennekam RC. Growth hormone analysis and treatment in Ellis-van Creveld syndrome. Am J Med Genet A. 2007;143a(18):2113–21.

Chapter 25
Spondyloepiphyseal Dysplasia

Lisa A. Cao and James T. Bennett

Background: Epidemiology and Pathophysiology

SED congenita is estimated to affect 1:350,000 children [1]. It has an autosomal dominant inheritance pattern. The genetic defect is in the *COL2A1* gene, which plays a role in synthesis of type II collagen [2]. Type II collagen is important in cartilage development and long bone formation.

SED tarda is estimated to affect 1:150,000–600,000 individuals [1]. It has an X-linked recessive inheritance pattern, thus males are almost exclusively affected by this disorder. This form is associated with the *TRAPPC2* gene [2]. TRAPPC2 is the abbreviation for trafficking protein particle complex subunit 2, which plays a role in transporting procollagen, the precursor in the process of chondrogenesis [3]. Additional mutations associated with the tarda form create structural abnormalities in type 2 collagen [4].

Clinical Presentation: History and Physical

Spondyloepiphyseal dysplasia translates into "abnormal spine and growth plate" in Latin. Therefore, patients with SED commonly have short statures with a short trunk and short extremities. As they progress throughout life, they tend to develop

L. A. Cao
Department of Orthopaedic Surgery, LAC+USC Medical Center, Los Angeles, CA, USA
e-mail: lisa.cao@med.usc.edu

J. T. Bennett (✉)
Department of Orthopaedic Surgery, Children's Hospital of Los Angeles, Los Angeles, CA, USA

Children's Surgical Specialty Group, Children's Hospital of the King's Daughters, Norfolk, VA, USA

J. F. Sarwark, R. L. Carl (eds.), *Orthopaedics for the Newborn and Young Child*,
https://doi.org/10.1007/978-3-031-11136-5_25

early arthritis in their large joints, including the hips, knees, and shoulders. They also commonly have back pain and occasionally respiratory complications from scoliosis [2]. They generally have normal cognitive development [4].

SED congenita is generally diagnosed at birth or early in infancy by expert clinical genetic consultation. They have characteristic facies that include flattening of their nasal bridge and cleft palate. Affected children should be referred to an ophthalmologist for evaluation of myopia. Less commonly, they are prone to experiencing retinal detachment and congenital cataracts. Patients also may experience hearing loss and should be evaluated by an otolaryngologist [4].

SED tarda is typically identified later in childhood because these patients are born with normal body proportions. Their growth deficiency is generally not apparent until school age (between 6 and 8 years) [5]. They also do not have the stigmata that are common in the congenital form (difficulty with eyesight and hearing).

Evaluation

If there is a clinical suspicion for SED, radiographs of the bones that are commonly affected including the entire spine and pelvis as well as a skeletal survey are recommended. Flexion and extension views of the cervical spine are important to rule out atlantoaxial instability and odontoid hypoplasia [4]. Platyspondyly (flattened vertebral bodies) may be apparent on lateral views of the spine with a characteristic rounding of the endplates [2, 4] (Fig. 25.1). Patients commonly have coxa vara

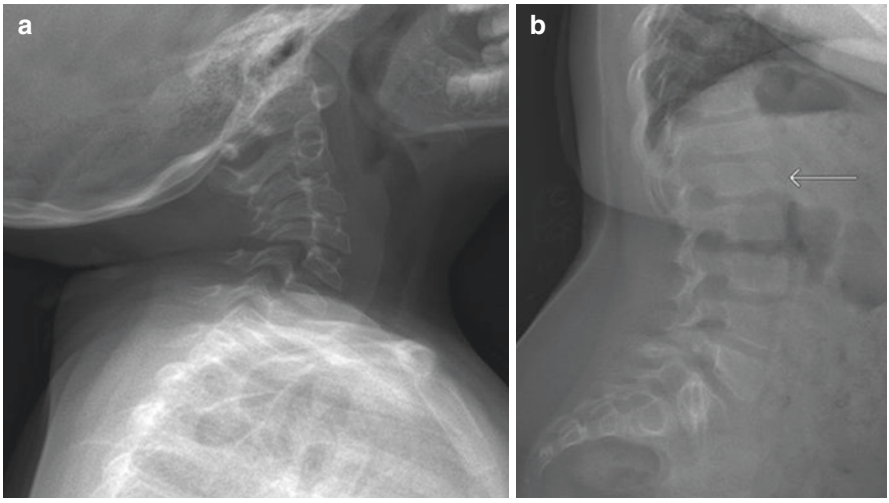


Fig. 25.1 Lateral radiographs of the cervical spine (**a**) demonstrating odontoid hypoplasia and lumbar spine, (**b**) demonstrating mild platyspondyly of vertebral bodies that is characteristic of SED. The white arrow indicates characteristic end plate abnormality. Used with permission from The Children's Orthopaedic Center at Children's Hospital Los Angeles

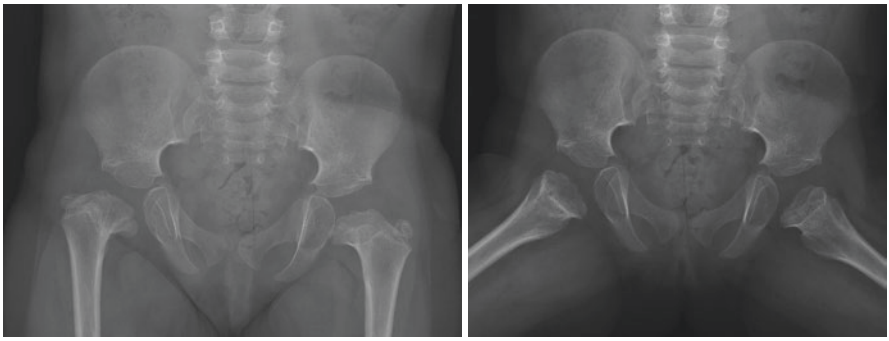


Fig. 25.2 AP and frog-leg lateral pelvis radiographs of a 6-year-old female pelvis (anterior-posterior and frog-leg) with SED demonstrating delayed ossification of bilateral femoral heads. Used with permission from The Children's Orthopaedic Center at Children's Hospital Los Angeles

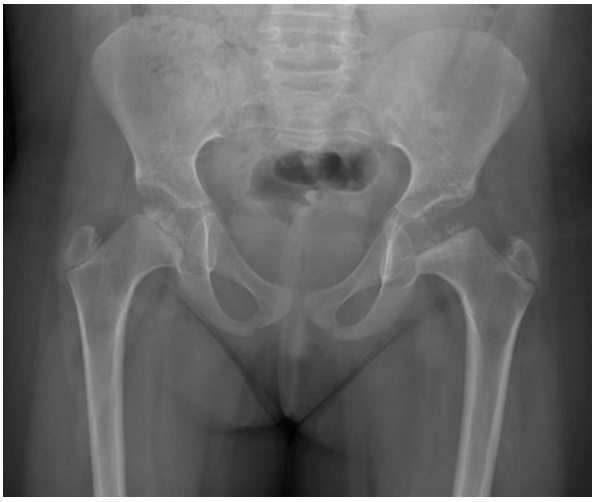


Fig. 25.3 AP pelvis radiograph of a 9-year-old female with SED demonstrating bilateral abnormal femoral head ossification centers. Used with permission from The Children's Orthopaedic Center at Children's Hospital Los Angeles

(decreased femoral neck-shaft angle) as a result of short femoral necks. Radiographs of the extremities will demonstrate abnormal-appearing growth plates and delayed appearance of ossification centers [6] (Figs. 25.2 and 25.3).

The radiographic imaging will distinguish SED from multiple epiphyseal dysplasia (MED), (a more common skeletal dysplasia that has very similar characteristics to SED). However, MED only involves the growth plates of long bones, as the spine is unaffected in MED. Both SED and MED have abnormal-appearing femoral heads that may be misperceived as femoral head avascular necrosis, also known as Legg-Calve-Perthes disease (LCP). Generally, LCP presents unilaterally; if affected bilaterally, the hips will often be in different stages of healing. This is in contrast to SED/MED, which demonstrates symmetric involvement of the femoral heads [6].

Referral to a geneticist is necessary for confirmatory testing. DNA analysis may be recommended to evaluate for the genetic mutation that led to SED.

Management

Symptomatic treatment is recommended for patients with SED. Children with the congenital form should be evaluated for eyeglasses and hearing aids. Parents should be advised that their child should not participate in high-energy or contact sports because of the risk of cervical instability and retinal detachment. Prior to any surgical intervention, the cervical spine should be re-evaluated given the high risk of atlantoaxial instability to decrease the risk of potential injury associated with manipulation of the cervical spine during intubation. Patients will commonly complain of arthralgia which may require pain medication and the help of a chronic pain specialist.

Parents should be warned to look for signs of myelopathy (gait imbalance or difficulty with fine motor skills) that may be indicative of atlantoaxial instability. If the patient has instability noted on the flexion-extension cervical spine series or has evidence of myelopathy or cord compression, spinal fusion is recommended.

SED patients are commonly affected by scoliosis, differentiating it from MED. The scoliosis may lead to compromised lung volume resulting in respiratory problems. Bracing is commonly the first line of treatment to prevent further progression. However, if the curve is greater than 50° or limiting normal pulmonary function, spinal fusion is recommended [6].

As mentioned previously, patients may frequently complain of joint pain, especially in their hips and knees. If there is significant hip dysplasia evident on radiographs, the patient may be a candidate for femoral and/or acetabular osteotomies in an attempt to delay early arthroplasty [6]. Regardless, patients commonly have progressive osteoarthritis that often require to total hip arthroplasty in their fifth decade of life [2].

Yearly follow-up with the patient's pediatrician, orthopedic surgeon, ophthalmologist, and otolaryngologist is recommended.

Clinical Pearls

- SED congenita has an autosomal dominant inheritance pattern and is associated with ocular and auditory abnormalities
- SED tarda has an X-linked recessive inheritance pattern, is often diagnosed later in childhood, and lacks ocular and auditory involvement
- SED patients have a high risk of atlantoaxial instability and require cervical spine evaluation prior to undergoing anesthesia
- Referral to an orthopedic surgeon is important for evaluation and management of early osteoarthritis and scoliosis

References

1. Wynne-Davis R, Gormley J. The prevalence of skeletal dysplasias. An estimate of their minimum frequency and the number of patients requiring orthopaedic care. J Bone Joint Surg Br. 1985;67:133–7.
2. Tiller GE, Hannig VL. X-linked spondyloepiphyseal dysplasia tarda. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews®. Seattle, WA: University of Washington, Seattle; 2001. p. 1993–2018.
3. Fukuma M, Takagi M, Shimazu T, Imamura H, Yagi H, Nishimura G, Hasegawa T. A familial case of spondyloepiphyseal dysplasia tarda caused by a novel splice site mutation in TRAPPC2. Clin Pediatr Endocrinol. 2018;27:193–6.
4. Terhal PA, Nievelstein RJ, Verver EJ, Topsakal V, van Dommelen P, Hoornaert K, et al. A study of the clinical and radiological features in a cohort of 93 patients with a COL2A1 mutation causing spondyloepiphyseal dysplasia congenita or a related phenotype. Am J Med Genet A. 2015;167A(3):461–75.
5. Whyte MP, Gottesman GS, Eddy MC, McAlister WH. X-linked recessive spondyloepiphyseal dysplasia tarda. Clinical and radiographic evolution in a 6-generation kindred and review of the literature. Medicine (Baltimore). 1999;78:9–25.
6. Herring JA, Tachdjian MO. Chapter 40—Skeletal dysplais. In: Tachdjian's pediatric orthopaedics. Philadelphia: WB Saunders; 2002.

Chapter 26
Juvenile Idiopathic Arthritis

Deirdre De Ranieri

Juvenile Idiopathic Arthritis (JIA) is the most common rheumatic disease of childhood, affecting over 300,000 children nationwide. Incidence of JIA in North America has been reported to be between 4 and 12 per 100,000 per year [1]. JIA is defined as arthritis that begins before the age of 16 years, persists for longer than 6 weeks, and cannot be explained by another process [2]. The hallmark feature of JIA is inflammation of the synovial lining within joints (arthritis or synovitis), around tendons (tenosynovitis), and at the insertion of tendons, ligaments, or capsule onto bone (enthesitis). The name assigned to childhood arthritis has undergone several permutations over the years, from JRA (Juvenile Rheumatoid Arthritis) to JCA (Juvenile Chronic Arthritis) to what we now call JIA (Juvenile Idiopathic Arthritis). These changes were instituted mostly to homogenize the subgroups for research purposes. Recently, in late 2018, a revised classification was proposed by the Pediatric Rheumatology International Treaty Organization (PRINTO), with the additional aim of distinguishing the forms of arthritis seen solely in childhood from the childhood forms that correlate with adult disease [3]. While there is work ongoing to validate this new classification system, the classification criteria that are currently being used are derived from the ILAR-defined classification criteria, which were devised in 2001 (Table 26.1) [2, 4].

There are currently seven defined subtypes of JIA, and there is significant heterogeneity among these subtypes. The categorization is based on a combination of clinical and laboratory factors that are determined during the first 6 months of disease [2]. Oligoarticular JIA is the most common subtype of JIA, defined by arthritis in four or fewer joints and is further subdivided into a persistent subtype (in which the disease never progresses beyond 4 joints) and an extended subtype (in which more than four joints become affected after 6 months of being diagnosed).

D. De Ranieri (✉)
Department of Pediatric Rheumatology, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA
e-mail: dderanieri@luriechildrens.org

J. F. Sarwark, R. L. Carl (eds.), *Orthopaedics for the Newborn and Young Child*,
https://doi.org/10.1007/978-3-031-11136-5_26

Table 26.1 ILAR Classification Criteria for JIA [4]. Reprinted with permission from Springer Nature, Beresford MW. Juvenile Idiopathic Arthritis: New Insights into Classification, Measures of Outcome, and Pharmacotherapy. *Paediatric Drugs*. Vol.13/Issue 3, pgs 161–73, © 2011

Subtype of JIA	Definition and exclusion criteria
Systemic JIA	Definition: • Arthritis in one or more joints, with or preceded by fever for ‡2 weeks' duration and documented "quotidian" (daily febrile paroxysms) for ‡3 days • Accompanied by one or more of the following: – Evanescent erythematous rash – Lymphadenopathy – Hepatomegaly and/or splenomegaly conditions – Serositis Exclusions: [a] a, b, c, d Notes: • Mandatory exclusion of infective and malignant causes • Arthritis may not be present early in the disease course
Oligoarticular JIA	Definition: • Arthritis of up to four joints during the first 6 months of disease Two sub-categories recognized: • Persistent: affecting up to four joints throughout the disease course • Extended: affecting a total of more than four joints after the first 6 months of disease Exclusions: [a] a, b, c, d, e
RF+ Polyarticular JIA	Definition: • Arthritis of five or more joints within the first 6 months of disease • Two or more tests for RF at least 3 months apart during the first 6 months of disease are positive Exclusions: [a] a, b, c, e
RF- Polyarticular JIA	Definition: • Arthritis of five or more joints within the first 6 months of disease • Test for RF is negative Exclusions: [a] a, b, c, d, e
Psoriatic JIA	Definition: • Arthritis and psoriasis, OR arthritis and two or more of the following: – Dactylitis – Nail pitting or onycholysis – Psoriasis in a first-degree relative Exclusions: [a] b, c, d, e
Enthesitis-related arthritis	Definition: • Arthritis and enthesitis, OR • Arthritis or enthesitis with two or more of the following: – Presence or history of sacroiliac joint tenderness and/or inflammatory lumbosacral pain – HLA B27 antigen – Onset of arthritis in a male over 6 years of age – Acute (symptomatic) anterior uveitis – History of ankylosing spondylitis, enthesitis-related arthritis, sacroiliitis with inflammatory bowel disease, Reiter's syndrome, or acute anterior uveitis in a first-degree relative Exclusions: [a] a, d, e

Table 26.1 (continued)

Subtype of JIA	Definition and exclusion criteria
Undifferentiated JIA	Definition: • Arthritis that fulfills criteria in no category or in two or more of the above categories

HLA human lymphocyte antigen; *RF* rheumatoid factor

[a] Exclusion criteria: (a) psoriasis or a history of psoriasis in the patient or a first-degree relative; (b) arthritis in an HLA B27-positive male beginning after the sixth birthday; (c) ankylosing spondylitis, enthesitis-related arthritis, sacroiliitis with inflammatory bowel disease, Reiter's syndrome, acute anterior uveitis, or a history of one of these disorders in a first-degree relative; (d) the presence of IgM RF on two or more occasions ≥3 months apart; (e) the presence of systemic JIA in the patient

Polyarticular JIA is defined by arthritis in five or more joints and is subdivided into RF+ polyarticular JIA and RF- polyarticular JIA. The presence or absence of RF must be determined on 2 occasions, at least 3 months apart. RF+ polyarticular disease is essentially childhood-onset rheumatoid arthritis and carries a similar prognosis [5]. In psoriatic JIA, among the defining criteria are arthritis and psoriasis. If these two criteria are not both met, a child must have arthritis and at least two of the following three criteria to be diagnosed with Psoriatic JIA: dactylitis, onycholysis or nail pitting, or first-degree family member with psoriasis. Enthesitis-related arthritis, which is commonly called juvenile spondyloarthropathy, is diagnosed based on the presence of both arthritis and enthesitis, or one of these two conditions with at least two of the following five criteria: sacroiliac joint tenderness and/or inflammatory lumbosacral pain, presence of two of the following: HLA-B27, onset in a male over the age of 8, acute anterior uveitis, or family history of an HLA-B27 mediated disease in a first or second degree relative. HLA-B27 mediated disease includes iritis, psoriasis, Ankylosing Spondylitis (AS), Reactive Arthritis (ReA), and Inflammatory Bowel Disease (IBD). Juvenile Ankylosing Spondylitis (JAS) is included in this subtype, and like the adult counterpart, is characterized by radiographic evidence of sacroiliitis [6]. Systemic JIA (sJIA), although categorized with the other subtypes, is a genetically and phenotypically distinct entity [7]. As opposed to the other JIA subtypes, which are considered auto-immune diseases, involving dysregulation of the humoral immune system, sJIA is considered an autoinflammatory disease resulting from a defect in the innate immune system [8]. The pathophysiology, clinical features, and treatment of sJIA differ from the other subtypes. sJIA is characterized by arthritis, at least 2 weeks of daily fever (at least 3 consecutive days of which should be quotidian), and at least one of the following characteristics: rash which is commonly described as "evanescent" and "salmon-colored" (although this can vary based on ethnicity), generalized lymphadenopathy, hepatomegaly and/or splenomegaly, and serositis (pleuritis and/or pericarditis). Undifferentiated JIA is a term ascribed to those individuals who do not fit into one of the aforementioned categories of JIA or who fit into more than one category.

Patients with JIA can be re-classified later into a different subtype later in their disease course, i.e., from oligoarticular persistent JIA to oligoarticular extended JIA, or from oligoarticular JIA to ERA subtype, etc., if the phenotype and/or

laboratory profile changes over time. Studies have found that 35–40% of patients with oligoarticular JIA (persistent subtype) were re-classified later in the disease course to oligoarticular JIA extended subtype secondary to additional joints becoming involved, and the prognosis of these children was similar to that of RF- polyarticular JIA [3, 9]. Early patterns of joint involvement in children with oligoarticular JIA, such as symmetric arthritis, and arthritis of the wrist and ankle have been associated with extension of the disease, need to use DMARDs, increased disease activity as well as erosive disease at follow-up. Both the wrist and the ankle are joint complexes, each being comprised of more than one joint, so it could be argued that involvement of either already constitutes polyarticular disease [3].

Epidemiology/Pathophysiology

JIA is a heterogeneous group of diseases that result from complex interactions between the immune system and numerous environmental factors in a genetically susceptible individual. This interplay results in immune-mediated inflammation of the synovium, which is found in joints, tendon sheaths, and entheses. The immune phenotype varies among the subtypes of JIA, with most of the subtypes associated with defects in the adaptive immune system, and systemic JIA resulting from defects in the innate immune system. Levels of immune-mediated cells vary per subtype. Upregulation of monocytes, macrophages, and neutrophils are seen in sJIA, as would be expected with involvement of the innate immune system, and T cell activation is more typically seen in the other subtypes of JIA consistent with defects in the adaptive immune system [10]. Several techniques including Genome Wide Association Studies (GWAS) and candidate gene studies of single nucleotide polymorphisms (SNPs) have enabled the identification of several Human Leukocyte Antigen (HLA) and non-HLA susceptibility loci in JIA. While there is thought to be less than a 20% heritability in JIA, over the past 20 years, there is increasingly more data being identified relating to the genetics underlying the pathophysiology of JIA. Some of these polymorphisms are shared with other rheumatologic diseases and others appear to be specific to JIA [11]. Sibling studies have revealed a concordance rate of between 25 and 40% in monozygotic twins compared to the prevalence in the general population of 1/1000, and interestingly, these children developed disease on average within 6 months of each other and almost all shared the same ANA status [12]. Similarly, in sibling pairs with JIA, there were several similarities, including sex, type of JIA, and age of onset. Additionally, in extended families of patients with JIA, there is a threefold increase in the frequency of autoimmune disease in general, suggesting common genetic susceptibility factors [11].

There are several well-described genetic associations in JIA, particularly in the oligoarticular and RF- polyarticular subtypes. There are strong associations with several HLA alleles such as HLA DRB1*11 as well as a protective effects of others, including HLA DRB1*15:01. Several other gene variants also harbor mutations associated with these two subtypes of JIA, including PTPN2, PTNP22, STAT4,

IL-2, IL2RA, IL-6, and IL-6R [11]. RF+ polyarticular JIA is genetically very similar to its adult counterpart, RA, with a similarly strong association with HLA DRB1 amino acid13 [5]. Non-HLA associations seen in RF+ polyarticular JIA include PTPN22, STAT4, and TNFAIP3 variants. ERA subtype of JIA is strongly associated with HLA-B27, as is psoriatic JIA [11]. The genetics of systemic JIA are different from the other subtypes, reflecting its different pathophysiology. Genetic associations with sJIA include HLA DRB1:04:05, DQB1:04:01. Non-HLA associations have also been found in sJIA and include polymorphisms of several genes encoding the pro-inflammatory cytokines IL-6, TNF-alpha, IL-1, and IL-10 [8].

Biomarkers are another evolving means of classifying and further risk-stratifying patients with JIA. There are no currently validated biomarkers in JIA, but research is ongoing in this field, and potential targets include cytokines such as TNF-alpha and IL-6 [13]. Biomarkers and how genetic and epigenetic data translate clinically will all contribute to the development of personalized medicine, in which treatment is based on a molecular understanding of disease phenotypes [14]. Correlating genetics and biomarkers with diagnosis, treatment choices, and outcome is on the horizon.

Clinical Presentation

Arthritis is a clinical diagnosis and is characterized by swelling, warmth, stiffness, limitation, and/or pain with range of motion. Morning stiffness and gelling (discomfort when moving after periods of inactivity, such as sitting, standing, lying, etc.) are frequent complaints in people with arthritis. The differential diagnosis for JIA is extensive and includes infection, malignancy, mechanical conditions, injury/trauma, endocrinopathies, gastrointestinal diseases, connective tissue diseases, and autoinflammatory syndromes. Some of the more commonly seen disease processes that can present in a similar fashion to JIA are noted in Table 26.2. Furthermore, there is significant heterogeneity in presentation among the seven different subtypes of JIA. For example, there are variations in the number of joints involved, typical age at diagnosis, extra-articular findings, family history, and lab profile (Table 26.3) [15].

Oligoarticular JIA is the most common subtype, affecting 40–50% of patients, preferentially affecting females, with a peak age of onset between 2 and 4 years. The distribution of arthritis in this subtype is usually asymmetric and typically involves large joints, such as knees, ankles, and elbows (Fig. 26.1). Tenosynovitis is a common finding in patients with ankle involvement, with up to one-third of patients having tenosynovitis as the sole cause of their ankle swelling. This is most readily visualized by ultrasound (Fig. 26.2). In general, pain is not a primary complaint in children with oligoarticular JIA, and they tend to continue performing their activities of daily life. Symptoms tend to be more prominent in the morning and include limping, refusal to walk, and wanting to be carried or put in a stroller. There is an increased incidence of anterior chamber uveitis in this population, with

Table 26.2 Other conditions that present with joint pain and swelling

Other conditions that may present with joint pain and swelling			
Disease entity	Demographics	Distinguishing features	Clinical pearls
Acute lymphocytic leukemia (ALL)	Preschool and school-aged children	May present with very painful joint swelling as well as bone and/or joint pain at night. Usually associated with fevers, night sweats, pallor, weight loss, and other B symptoms	Initial CBC and bone marrow biopsy may be normal. It is important to repeat these studies if clinical suspicion remains high
Benign Joint Hypermobility Syndrome (BJHS)	Late preadolescents and early adolescent F < M	Diffuse musculoskeletal pain, often worse with activity and better with rest May see trace effusions, but there should not see synovitis	Pain out of proportion to physical exam findings Hypermobile joints on exam
Pediatric fibromyalgia	Late preadolescence through adolescence F > M	Chronic widespread pain for at least 3 months. Tender points less reliable in children	Associated with poor sleep, anxiety, depression Positive family history is common
Apophysitis (e.g., Osgood-Schlatter disease)	School-aged children and adolescents	Localized pain, exacerbated by activity and better with rest	Tenderness and swelling at the affected apophysis Enthesitis can present similarly
Infectious arthritis	Any age	Acute onset of pain, especially with movement Often have fevers, rash, abnormal labs depending on infectious etiology	Arthrocentesis **necessary** to evaluate synovial fluid (culture, cell count, gram stain, etc.) Lyme disease testing needed in patients with monoarticular arthritis Sexual history important if considering gonococcal arthritis
Acute Rheumatic Fever (ARF)	Ages 5–15	Painful, migratory arthritis Responsive to NSAIDs Very elevated CRP, ESR	Antibiotics are necessary to prophylaxis against carditis. Duration depends on age and presence or absence of carditis
Post-Streptococcal Reactive Arthritis (PSRA)	Ages 5–15	Additive arthritis, non-migratory Less responsive to NSAIDs	Prophylactic antibiotics for 1 year provided echocardiogram at cessation of treatment is normal

Table 26.2 (continued)

Other conditions that may present with joint pain and swelling			
Disease entity	Demographics	Distinguishing features	Clinical pearls
Inflammatory Bowel Disease (IBD) associated arthritis	Peak onset of IBD diagnosis is in adolescence Up to 70% of patients with IBD develop arthritis	Usually affects lower extremity, large joints Can also affect the SI joints and spine Less frequently involves smaller joints	Colitis and arthritis may occur independently of each other or in parallel Treatment is the same for both disease processes
Connective tissue disease (i.e., lupus, dermatomyositis, scleroderma)	Variable, usually >5 years old	MSK complaints are common, often have skin findings, B symptoms, and/or abnormal labs	History, physical exam findings, labs will direct diagnosis and treatment

upwards of 20% of patients with oligoarticular JIA and a positive ANA developing uveitis over time.

RF- polyarticular JIA affects approximately 20% of children with JIA and has a bimodal presentation, presenting either between ages 1 and 3 or in adolescence. Patients who present earlier tend to be female, have a positive ANA, and are at increased risk of uveitis. The patients in the later onset group are also predominantly female, but have a lower rate of ANA positivity and a lower risk of developing uveitis [16]. This disease affects large or small joints and is typically symmetric (finger, hands, knees, ankles, etc.). There is a higher risk of temporomandibular joint (TMJ) arthritis in this subgroup of JIA compared to the other subgroups. TMJ arthritis is often asymptomatic and physical exam findings can be very subtle, such as mild mandibular asymmetry and decreased mouth opening capacity. This can lead to under-diagnosis, which may result in the development of physical deformities over time (micrognathia, retrognathia causing the classic "bird-face deformity," noted in Fig. 26.3), as well as functional disability (including anterior open bite). It has been estimated that between 40 and 100% of patients have TMJ involvement [17–19]. MRI with and without contrast is the gold standard for evaluating TMJ synovitis (Fig. 26.4). There are currently no screening guidelines for TMJ imaging in JIA, and it is up to the discretion of the treating pediatric rheumatologist whether or not to obtain an MRI. In addition to the increased risk of TMJ arthritis in RF- polyarticular JIA, there is also an increased risk of uveitis, similar to that seen in oligoarticular JIA, particularly in those who are ANA+.

RF+ polyarticular JIA, which accounts for less than 5% of all subtypes of JIA, usually affects children in their early teens. These patients present with arthritis in a similar joint distribution to that seen in RF- polyarticular JIA (bilateral and symmetric, usually affecting the small joints of the hands and feet). This disease has the same prognosis as the adult disease, rheumatoid arthritis, tending to flare and remit throughout childhood and adulthood. Indeed, the genetics underlying these two diseases are very similar. There is a higher risk of erosive joint disease and functional disability in this subtype of JIA, especially if they also have a positive anti-cyclic citrullinated peptide (anti-CCP) antibody.

Table 26.3 Characteristics of JIA [15]. Reprinted from Pediatric Clinics of North America, Vol. 59/Issue 2, Gowdie PJ, Tse SM, Juvenile idiopathic arthritis, pgs 301–327, © 2012, with permission from Elsevier

ILAR JIA subtype	Sex, age, and % total patients with JIA	Typical joint involvement	Occurrence of uveitis	Other features
• Oligoarticular • Persistent • Extended	F > M Early childhood 40–50%	≤4 joints Large joints: knees, ankles, wrist Persistent disease: never >4 joints affected Extended disease: involves >4 joints after first 6 months of disease	Common (30%) especially if ANA positive Usually asymptomatic	ANA 60–80% positive
Polyarticular (RF-negative)	F > M 2 peaks: 2–4 years and 6–12 years 20–25%	≥5 joints Symmetric	Common (15%)	ANA 25% positive ± C spine and TMJ
Polyarticular (RF-positive)	F > M Late childhood/ early adolescence 5%	Symmetric small and large joints Erosive joint disease	Rare (<1%)	ANA 75% positive Rheumatoid nodules
Systemic	M = F Throughout childhood 5–10%	Poly or oligoarticular	Rare (<1%)	Daily (quotidian) fever for ≥2 weeks Evanescent rash Lymphadenopathy Hepatosplenomegaly Serositis
Enthesitis-related arthritis	M > F Late childhood/ adolescence 5–10%	Weight-bearing joint especially hip and intertarsal joints History of inflammatory back pain or sacroiliac joint tenderness	Symptomatic acute uveitis (~7%)	Enthesitis HLA-B27-positive Axial involvement (including sacroiliitis) Family history of HLA-B27-associated disease

Table 26.3 (continued)

ILAR JIA subtype	Sex, age, and % total patients with JIA	Typical joint involvement	Occurrence of uveitis	Other features
Psoriatic arthritis	F > M 2 peaks: 2–4 years and 9–11 years 5–10%	Asymmetric or symmetric small or large joints	Common (10%)	Nail pits, onycholysis Dactylitis Psoriasis Family history psoriasis
Undifferentiated	10%			Does not fulfill criteria for any above category or fulfills criteria for >1 category

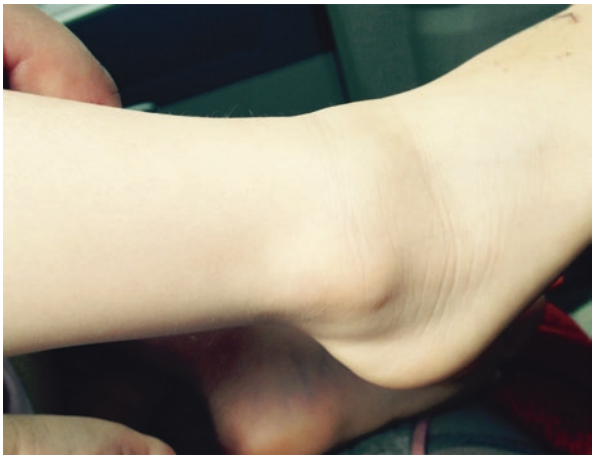


Fig. 26.1 Ankle swelling in a 4-year-old girl with oligoarticular JIA. Note the fullness around the anterior ankle, suggestive of a tibiotalar effusion, as well as around the lateral malleolus, suggestive of tenosynovitis of the lateral ankle tendons

Enthesitis-related arthritis (ERA) accounts for up to 10% of patients with JIA, preferentially affects males and typically presents with an asymmetric oligo- or polyarthritis arthritis, usually involving the lower extremities. Enthesitis refers to inflammation at the site of attachment of ligaments, tendons, or joint capsule to bone. Commonly affected sites of enthesitis in children include the heel and foot, at the sites of insertion of both the Achilles tendon and plantar fascia, as well as the knee, at the sites of attachment of the quadriceps and patellar tendons [20]. Enthesitis is well-visualized on ultrasound (Fig. 26.5). Axial disease involving the spine and sacroiliac (SI) joints is common in ERA, often presenting with stiffness and pain in the lower back. Juvenile Ankylosing Spondylitis (JAS) is in the family of ERA and is characterized by radiographic evidence of spinal involvement (in either the SI joints or spine) (Fig. 26.6). Finally, ERA may coexist with Inflammatory Bowel Disease (IBD) and be the presenting feature of this disease.

Enthesitis and axial disease are also common in psoriatic JIA, particularly in older male children. Psoriatic arthritis constitutes 5–10% of patients with JIA,

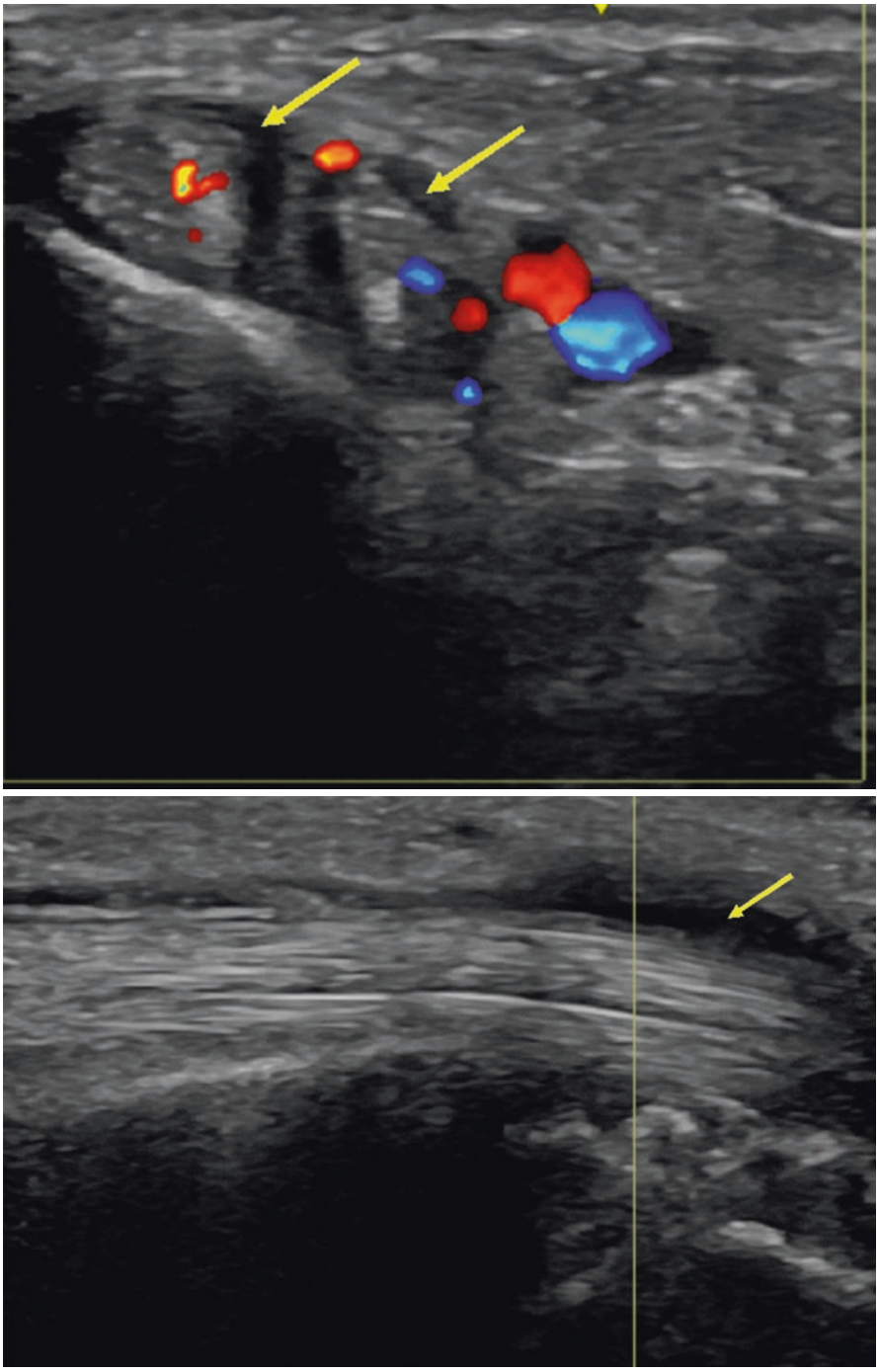


Fig. 26.2 4-year-old girl with oligoarticular JIA presenting with tenosynovitis of the flexor tendons. Top (medial transverse view at level of medial malleolus): note the anechoic rim around the posterior tibial tendon and the flexor digitorum (yellow arrows) with positive CPD. Bottom (medial longitudinal view of the same tendons): note the wavy anechoic material superficial and deep to the posterior tibial tendon (yellow arrow)

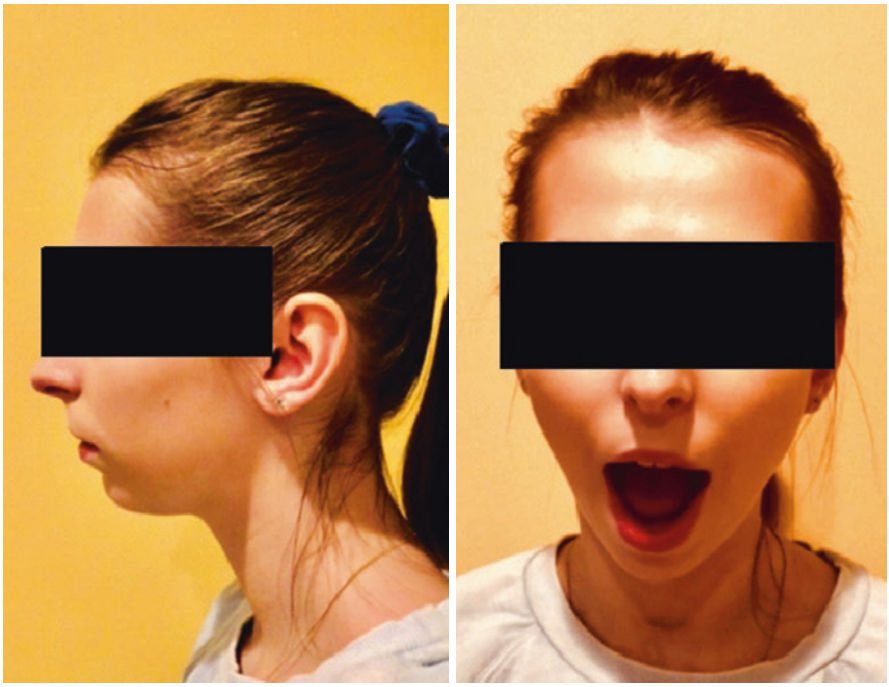


Fig. 26.3 14-year-old girl with RF- polyarticular JIA. Note the small, recessed mandible (image on left) as well as an asymmetric oral opening with right-sided deviation (image on right)

depending on the population studied and typically has a bimodal distribution with an early peak around ages 2–4 and a later peak in adolescence [20]. The younger cohorts tend to be female, have a peripheral asymmetric arthritis often involving the small joints, dactylitis is common, and these patients are at higher risk for uveitis, particularly if they are ANA positive [21]. Later onset psoriatic JIA resembles adult onset psoriatic arthritis, with a greater percentage of males affected and higher incidence of sacroiliitis and enthesitis [22]. Adiposity is also increased in this subgroup, and it has been shown that patients with psoriatic JIA are 50% more likely to be overweight than patients with RF+ polyarticular JIA [23]. This is similar to what is seen in adult psoriatic arthritis, where there is in a known increased risk of metabolic syndrome. Another similarity between the two groups is the association of microtrauma with disease flare. There are several case reports and case series that suggest a role for injury in the subsequent development of psoriatic arthritis and psoriatic JIA [24] in addition to [25].

Systemic JIA makes up approximately 10% of the patients with JIA and affects males and females equally, with an average age of onset between 4 and 5 years old [26]. Unlike the other subtypes of JIA, sJIA manifests with symptoms of systemic inflammation such as rash, fever, hepatosplenomegaly, generalized lymphadenopathy, and serositis [2]. Interestingly, arthritis may not always be present initially, sometimes occurring weeks to months after the onset of systemic features [27]. This

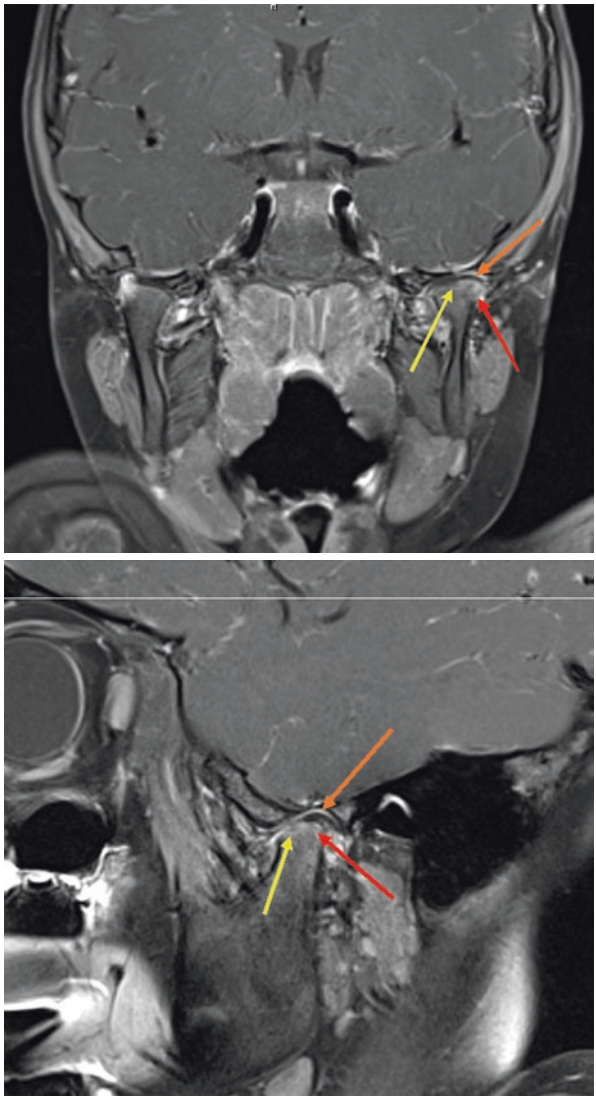


Fig. 26.4 Contrast-enhanced TMJ MRI of a 7-year-old male with RF- polyarticular JIA. Note enhancement of the synovium (orange arrow), bone marrow edema (red arrow), and small mandibular erosion (yellow arrow) noted on the coronal view of the left TMJ. Same findings noted on sagittal view. Right side is normal: no enhancement of the synovium, no bone marrow edema, no cortical irregularity

can lead to diagnostic delays as the differential diagnosis of fevers and rash is quite broad and includes entities such as infection and malignancy. Often, invasive procedures such as lumbar punctures and bone marrow biopsies as well as PET scans and CTs which involve a significant amount of radiation are necessary to investigate other potential etiologies. The laboratory profile in sJIA reflects significant inflammation, including elevated inflammatory markers, leukocytosis, thrombocytosis, anemia, hyperferritinemia, and hyperfibrinogenemia. Autoantibodies are not typically present initially, however there are reports of positive ANA and RF developing later in the disease process, suggesting possible evolution over time to a more

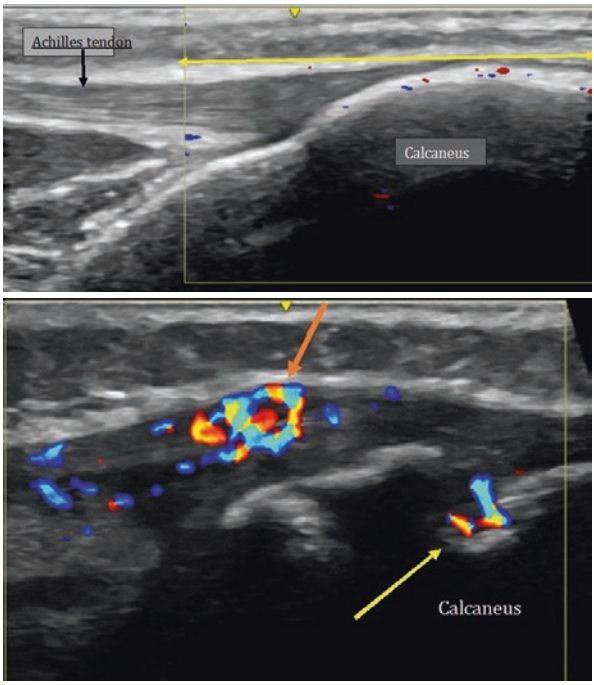


Fig. 26.5 Normal Achilles enthesis on top (yellow line shows length of enthesis). Achilles enthesitis below (Color Doppler signal within tendon close to its insertion), with erosive changes to the calcaneus (yellow arrow) and thickening of the Achilles tendon (orange arrow) in a 15-year-old boy

autoimmune phenotype [28]. In approximately, 10% of patients with systemic JIA, their disease is complicated by a process called Macrophage Activation Syndrome (MAS), which is considered a secondary form of Hemophagocytic Lymphohistiocytosis (HLH). This hyperinflammatory state resulting from dysregulation of the immune system and is characterized by T cell expansion and macrophage activation which in turn leads to hypersecretion of pro-inflammatory cytokines. Clinical findings include fever, splenomegaly, CNS dysfunction, and hepatomegaly and labs may reveal hyperferritinemia, liver dysfunction and coagulopathy, hypofibrinogenemia, elevated d-dimer as well as pancytopenia. It is important to note that in systemic JIA, there may be a *relative* decrease in WBC, platelets, and ESR in patients who are highly inflamed with baseline leukocytosis, thrombocytosis, and hyperfibrinogenemia, and that this is not normalization but rather a sign of evolving MAS [29]. It is crucial to recognize and treat MAS early and aggressively, as it is associated with a mortality rate between 8 and 23% [30].

The final subtype of disease, undifferentiated arthritis accounts for between 10 and 20% of patients with JIA, and the patients either fulfill no inclusion criteria or more than one inclusion criteria.

An important extra-articular manifestation of JIA is anterior chamber uveitis, which complicates 12% of all cases of JIA and 20% of cases of ANA+ oligoarticular JIA. Aside from a positive ANA, other risk factors for uveitis include young age at diagnosis, female sex, and oligoarticular JIA subtype. Uveitis refers to inflammation of the "uveal" components of the eye, which include the iris, choroid, and

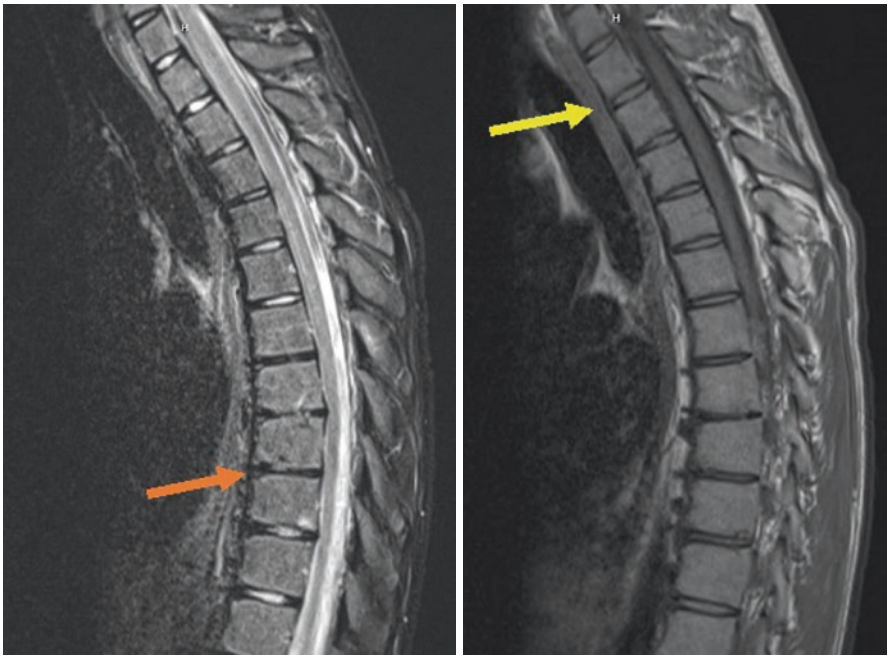


Fig. 26.6 16-year-old male with Juvenile Ankylosing Spondylitis (JAS). Left image (T2W STIR) shows erosions on the anterior corners of multiple mid-thoracic vertebrae (orange arrow). Right image (T1W STIR) shows early syndesmophyte formation on the anterior aspect of the upper thoracic vertebrae (yellow)

retina. Anterior chamber uveitis refers to inflammation superficial to the lens and can affect the iris and ciliary body [31]. Uveitis in this context is insidious, with up to 75% of patients being asymptomatic. Furthermore, young children are often unable to articulate the subtle visual changes that are associated with this disease, such as floaters, halos around lights at night, and cloudy vision. Frequent screening is recommended in young children [32]. Patients with RF- polyarticular JIA have the same risk profile for developing uveitis as extended oligoarticular JIA, with a young age of onset, positive ANA, and female sex being associated with increased risk of developing uveitis. However, children with RF+ polyarticular JIA have a very low risk of developing uveitis. In contrast to the insidious nature of the uveitis in the aforementioned subtypes, in both ERA and psoriatic JIA, uveitis is symptomatic and termed, "acute anterior uveitis," and manifests with acute pain, redness, and photophobia. Systemic JIA is not typically associated with uveitis. Complications of uveitis include synechiae, band keratopathy, cataracts, glaucoma, macular edema and potentially, blindness, if not recognized in a timely manner or treated aggressively (Fig. 26.7) [31]. Frequent examinations, particularly in young, female, ANA+ patients with oligoarticular JIA are recommended. Interestingly, disease activity in uveitis does not parallel that of uveitis; JIA can be in remission while uveitis is flaring and vice versa. Uveitis is a life-long complication in JIA requiring regular screening for life (Table 26.4) [32, 33].

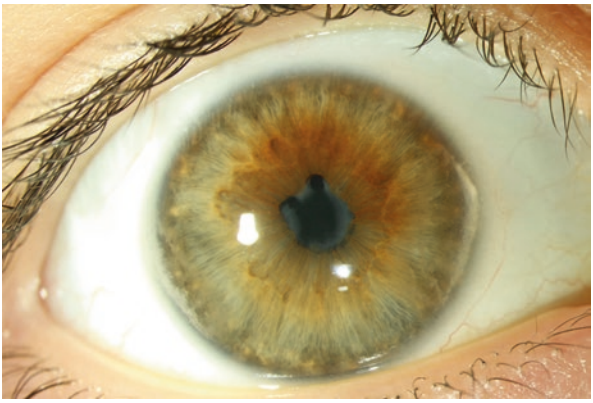


Fig. 26.7 Posterior synechiae in a 10-year-old girl with JIA and anterior chamber uveitis. Note the irregularly shaped pupil resulting from adhesions between the iris and the posterior lens. Note also the inflammatory cells in the anterior chamber, seen adjacent to medial and lateral edge of the iris. Photo courtesy of Dr. Debra Goldstein, Northwestern University

Table 26.4 Uveitis Screening Guidelines in Patients with JIA [32]. Reprinted from Heiligenhaus A, Niewerth M, Ganser G, Heinz C, Minden K; German Uveitis in Childhood Study Group. Prevalence and complications of uveitis in juvenile idiopathic arthritis in a population-based nation-wide study in Germany: suggested modification of the current screening guidelines, Rheumatology, ©2007, Vol. 46/Issue 6, pgs. 1015–19, by permission of Oxford University Press

JIA subgroup	ANA	Age at JIA onset (years)	JIA duration (years)	Recommended screening intervals (months)
OA, RF- PA, PsA, AA	+	≤6	≤4	3
OA, RF- PA, PsA, AA	+	≤6	>4	6
OA, RF- PA, PsA, AA	+	≤6	≥7	12
OA, RF- PA, PsA, AA	+	>6	≤2	6
OA, RF- PA, PsA, AA	+	>6	>2	12
OA, RF- PA, PsA, AA	–	≤6	≤4	6
OA, RF- PA, PsA, AA	–	≤6	>4	12
OA, RF- PA, PsA, AA	–	>6	n.a.	12
ERA	n.a.	n.a.	n.a.	12
RF+ PA, Sys A	n.a.	n.a.	n.a.	12
Patients with uveitis	n.a.	n.a.	n.a.	According to uveitis course

Sys A systemic arthritis; *OA* oligoarthritis; *RF- PA* seronegative polyarthritis; *RF+ PA* seropositive polyarthritis; *ERA* enthesitis-related arthritis; *PsA* psoriatic arthritis; *AA* other arthritis; *n.a.* not applicable

Work-Up

Initial evaluation of arthritis should rule out other etiologies such as infection and malignancy, with appropriate work-up depending on the clinical presentation. Laboratory studies are not helpful in diagnosing JIA, as it is a clinical diagnosis; however, several blood tests are important in defining disease subtype. ANA positivity is seen most commonly in oligoarticular JIA and RF- polyarticular JIA. It is associated with an increased risk of anterior chamber uveitis in these populations. A positive RF is seen in less than 5% of patients with JIA, and autoantibodies directed against cyclic citrullinated peptide (CCP) are seen in a similar percentage. Both of these autoantibodies are associated with a higher risk of erosive disease, joint damage, and functional disability [5]. HLA-B27 is a genetic marker associated with ankylosing spondylitis, and more than 90% of adults with AS are HLA-B27 positive. In ERA, the frequency of HLA-B27 positivity is between 50 and 75% [34]. Inflammatory markers are of limited utility in most subtypes of JIA, with the exception of sJIA, where fluctuations in inflammatory markers, ferritin levels, liver function tests, and cell counts can be indicative of either evolving or resolving disease.

Imaging is frequently used in JIA, to diagnose and treat arthritis, enthesitis, and tenosynovitis. It is also used to monitor disease activity, which is helpful as patients start, stop, and transition between medications. The most basic imaging technique that is used in evaluating patients with JIA is conventional radiography. X-rays are quick, cheap, and readily available at most facilities. A limitation of radiographs is the inability to show active disease, however, they are helpful in evaluating for chronic disease, such as joint space narrowing, osteopenia, erosions, and leg length discrepancies. Given the risks of radiation, CT is not a frequently used imaging modality in JIA. MRI and ultrasound are the gold standards for evaluating disease activity and response to therapy. MRI will provide a complete assessment of the joint, including the ligaments and tendons, and is the imaging modality of choice when evaluating the TMJ and SI joints. It is an expensive procedure, however, and often requires sedation and IV contrast, both of which are associated with risks. Musculoskeletal ultrasound (MSUS) is being used increasingly more in the field of rheumatology to evaluate joints, tendons, and entheses and is used to diagnose, monitor, and treat JIA (via IACI). Synovitis is easily demonstrated using this imaging modality (Fig. 26.8), and compared to MRI, it is significantly cheaper, faster, more easily accessible, and does not require the use of sedation or IV contrast. In addition to providing evidence of disease activity, it is also useful in evaluating clinical response to medication. MSUS is used to detect subclinical synovitis as well, and in adults with RA, these findings have been shown to predict disease progression [17, 35]. Studies evaluating the significance of subclinical synovitis in children with JIA are underway. Patients with JIA in remission have been shown to exhibit synovitis on MSUS, predominantly in the extended oligoarticular and polyarticular subtypes [36, 37]. While it is unclear if these joints progress to become damaged/symptomatic due to lack of literature on this subject in JIA, it is known that in RA, clinically inactive joints that harbor positive Doppler signal in the

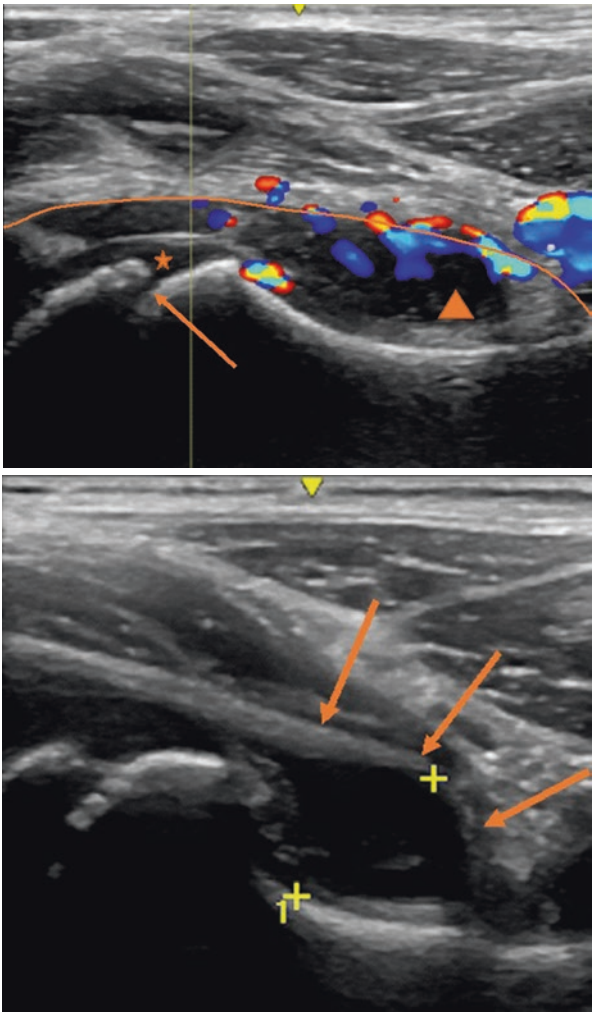


Fig. 26.8 Top image: MSUS with Doppler of a pediatric hip in an 8-year-old boy. Note the distended joint capsule (orange outline) and hypertrophied hypoechoic synovium (orange triangle and extending proximally). Cartilage is anechoic (orange star) until it ossifies, and the growth plate is still open (orange arrow). Synovitis of the hip joint is evidenced by positive Color Doppler (blue, red, yellow). Bottom image: MSUS of a pediatric hip effusion. Note the distended capsule (orange arrows). The Femoral Neck to Outer Capsule distance (FNOC) is indicated by the two yellow plus signs. Normal FNOC distance varies by age, ranging from 4 mm in toddlers to 7 mm in adults

synovium are at higher risk for relapse/progression [38]. MSUS cannot visualize structures deep to bone, so it is an inappropriate imaging modality to evaluate the SI joints and TMJ joints, as a significant percentage of these joints would be inaccessible. MRI is better suited to evaluate these joints. From a therapeutic standpoint, MSUS is also used for procedural guidance. Ultrasound-guided injections are more accurate than palpation guided-injections and are associated with less procedural pain [39]. Unless a child has severe anxiety surrounding needles or is getting multiple injections, these can often be performed in the office, using local anesthesia and the assistance of child life. Hips, SI joints, and the TMJ are often approached using fluoroscopic or CT-guidance to confirm intra-articular placement of the needle, but these procedures can be safely performed using ultrasound [40], thus saving the patient unnecessary radiation.

Treatment

Optimal therapy for JIA varies based on the subtype of disease, the number and type of joints involved, and laboratory findings. Non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids (both systemic and intraarticular), as well as biologic and non-biologic disease-modifying anti-rheumatic drugs (DMARDs) are the current treatment options in childhood arthritis, and the choice often depends on the severity of the arthritis and/or the refractory nature of the disease.

Non-steroidal anti-inflammatory drugs (NSAIDs) are often used as first-line therapy in children with arthritis, however the utility of NSAID monotherapy in most subtypes of JIA is unclear [41] and most patients need more aggressive therapy to control their arthritis. In adults with spondyloarthropathies, NSAIDs may decrease the risk of radiographic progression in patients with ankylosing spondylitis [42], and while they are recommended as first-line therapy in children with sacroiliitis [43] in conjunction with PT, the effect on radiographic progression is unclear due to lack of published literature on the topic.

Corticosteroids are used both systemically and intraarticularly in JIA. Systemic corticosteroids are primarily used in sJIA to expeditiously control inflammation. They have been used in conjunction with methotrexate and TNF-inhibitors as components of early aggressive therapy, which has been shown to induce remission earlier and maintain remission longer. A short course may also be considered for children with refractory polyarticular disease who are flaring, and it may take a month or two for a new DMARD to take clinical effect [41]. Otherwise, systemic corticosteroids are used sparingly and in conjunction with other DMARDs, as they are associated with several long-term adverse side effects, such as growth suppression, pubertal delay, and decreased bone mineral density [44]. Corticosteroids are also associated with other growth abnormalities in JIA, such as leg length discrepancies, which can cause gait abnormalities and lower back pain [45]. Common short-term side effects include weight gain, acne, emotional lability, sleep disturbance, and elevated intraocular pressure. Intra-articular corticosteroid injections (IACI) play a larger role in the treatment of arthritis in JIA, and while they are not associated with the same long-term risks, they can be associated with short-term side effects such as facial flushing, emotional lability, and sleep disturbance. IACI is often used as first-line therapy in children with JIA and can often induce long-standing remission. In the U.S., triamcinolone acetonide is commonly used. Triamcinolone hexacetonide is a longer-acting, more efficacious glucocorticoid, compared to triamcinolone acetonide [46] and is associated with decreased systemic effects, such as flushing, nausea, and weight gain. However, it is not currently FDA approved for use in the United States. The use of IACI as bridging or adjunctive therapy when transitioning medication is also a common practice, as some medications may not take clinical effect for up to 3 months. The role of IACI for the TMJ has been debated recently, with some recent data suggesting it be used only after failing systemic therapy, given the risks of the procedure such as heterotopic bone formation, and the lack of data supporting its long-term efficacy [17].

Non-biologic, or conventional, DMARDs are commonly used as monotherapy or concurrent therapy in the treatment of JIA. Methotrexate is the most commonly used DMARD, and it was the first medication to alter the course of arthritis in adults with rheumatoid arthritis [47]. Soon after, it was also found to be effective in children. Its use is recommended in children with oligoarticular JIA who have failed NSAIDs and/or IACI and is standard management (either as monotherapy or in conjunction with a biologic DMARD) in patients with polyarticular JIA. It has also been used in children with systemic JIA in whom arthritis is a cardinal feature of their disease. However, its use in sJIA has been on the decline since the introduction of the biologic medications that target IL1 and IL6. Side effects of methotrexate include immunosuppression, bone marrow suppression, and liver toxicity. A complete blood count and liver function tests should be drawn before starting methotrexate and every 3 months while on methotrexate to evaluate for medication toxicity. Sulfasalazine is another commonly prescribed DMARD in the treatment of JIA and may be more effective than methotrexate in treating peripheral arthritis in patients with spondyloarthropathies, such as one would see in the ERA subtype of JIA, which is the only subtype in JIA in which its use is supported over methotrexate [48]. GI distress is the most commonly seen side effect of sulfasalazine, but liver toxicity and myelosuppression can also occur. Although rare, sulfasalazine has also been associated with significant cutaneous eruptions, including Steven's Johnson Syndrome. Leflunomide is another DMARD that is used to treat arthritis. It is used sparingly in the treatment of JIA, as its efficacy is similar to methotrexate, however the side effect profile is less favorable, including increased risk of transaminitis, teratogenicity, and ILD [49]. Hydroxychloroquine is frequently used in adults with arthritis as part of "triple therapy" (in conjunction with methotrexate and sulfasalazine), but its routine use is not supported in JIA. Other DMARDs such as cyclosporine, azathioprine, and mycophenolate mofetil are infrequently used in the treatment of JIA.

Biologic DMARDs (commonly known as "biologics") were introduced in the 1980s and have revolutionized the treatment of JIA. There have been several randomized controlled trials in JIA that have reinforced the superiority and safety of these medications in the treatment of JIA [50]. The most commonly used biologic therapies are the TNF-inhibitors, and the three most commonly used are adalimumab (Humira), etanercept (Enbrel), and infliximab (Remicade). These drugs vary in the strategies they employ to block TNF, with adalimumab and infliximab being monoclonal antibodies against TNF, and etanercept being a receptor antagonist of TNF. They are given subcutaneously (adalimumab and etanercept) or intravenously (infliximab). TNF-inhibitors appear to be safe and effective in children with JIA and are used most frequently in the polyarticular subtype of JIA. The safety of these medications was called into question in 2008 when the FDA placed a black box warning on the medication, alerting consumers to the risk of malignancy associated with TNF-inhibitors. Subsequently, large database studies comparing the risks malignancy in those treated with TNFs compared to those treated with conventional DMARDs revealed no difference [51]. However, there have been adverse events reported such as opportunistic infections Hodgkin lymphoma, optic neuritis,

drug-induced lupus, and psoriasis. In general, TNF-inhibitors are considered second or third line treatments after NSAIDs and DMARDs; however, in axial disease (such as one may see in ERA), they are considered second line, after a trial of NSAIDs and physical therapy. Non-biologic DMARDs are relatively ineffective in treating axial disease [52]. Combination therapy with methotrexate and a TNF-inhibitor has been shown to bring children into remission faster than methotrexate alone and keep them in remission longer [53]. Earlier aggressive therapy, with DMARDs, TNF-inhibitors plus/minus a tapering dose of prednisone has been shown to induce clinically inactive disease faster and maintain patients in remission longer than DMARDs alone [54]. Data suggests that there is a window of opportunity early in the disease process that, when targeted with aggressive therapy, results in a more expedient and sustained remission [55].

There are several other biologics that are effective in treating arthritis in JIA. Abatacept is a molecule that impairs T cell activation by interfering with T and B cell co-stimulation and thus dampens the immune response [56] and is effective in children with polyarticular JIA. Tocilizumab is a monoclonal antibody to IL-6, which is one of the main players in driving inflammation and is used in the treatment of both polyarticular JIA and systemic JIA. Both abatacept and tocilizumab are available in intravenous and subcutaneous forms. Anakinra is a receptor antagonist to IL-1 and is very effective in controlling the systemic features seen in systemic JIA (as opposed to tocilizumab, which tends to be more effective in controlling the articular features in patients with systemic JIA) [55]. Anakinra has not been found to be useful in other subtypes of JIA. Rituximab is a chimeric monoclonal antibody to CD20, which is present only on B cells, and is used in patients with RF+ and/or CCP+ polyarticular JIA. Some patients with RF- polyarticular JIA also respond to B cell depletion with rituximab [55]. Rituximab is given as an IV infusion (2 doses, 2 weeks apart) every 6 months. Janus kinase (JAK) inhibitors (i.e., tofacitinib) are newer oral biologic medications that are approved in the treatment of RA and are currently in phase 3 trials for the treatment of polyarticular JIA, and the results are promising [57]. There are other biologics that are being used to treat arthritis, however trials need to be performed in children in order for them to be approved for JIA. Patents on the original biologics have started expiring, so "biosimilars" have entered the market as a lower cost alternative to biologics. Biosimilars are very similar in molecular composition to the original biologics but less expensive. They are expected to take up an increasing share of the biologic market [58].

Fortunately, many of these medications are also used to treat JIA-associated uveitis. Methotrexate and TNF-inhibitors are the most frequently used medications in the treatment of uveitis refractory to topical steroids. The monoclonal antibodies such as adalimumab and infliximab are superior to the receptor antagonists such as etanercept in this disease. Abatacept, tocilizumab, and rituximab have also been used successfully in the treatment of refractory uveitis [59].

The safety profile of biologics is generally reassuring. For example, etanercept was not associated with a significantly increased risk of adverse events over methotrexate alone [60]. Non-opportunistic infections have been reported with abatacept, transaminitis, and injection reactions with anakinra, and both a low rate of

infections and of transaminitis have been reported with tocilizumab. However, these adverse events are rare. Also, interestingly, although anakinra is used to treat MAS, there have been reports of anakinra also triggering MAS [61]. While the relative risk profile of biologics is considered low, we will have a better understanding over time, as we have more data to analyze regarding reported SAEs with these medications.

Aside from pharmacologic therapy, adjunctive therapies that are very important in maintaining function in patients with JIA include physical, occupational, and emotional therapy. The goal of physical and occupational therapy is to regain function, strength, and mobility so children can successfully resume activities of daily life. A study from 2009 reported that half of young adults with JIA continue to experience active disease and greater than one third have detectable degrees of disability and many continue to report growth disturbance [62]. Fortunately, recently, there has been a pronounced improvement in functional disability in patients with JIA, likely reflective of the improved treatments that are now available, however chronic pain scores remain elevated in these patients [63]. To promote normal social development, school attendance should be prioritized as well as extra-curricular and peer-group activities. Incorporating a pediatric counselor or psychologist can have a beneficial impact on children with JIA as they learn to healthily navigate the world in the context of having a chronic disease [41].

Outcome measures in JIA have increasingly included patient or parent reported outcomes (PRCOs) in which issues that are important to the patients and their parents are brought to the forefront. Types of PRCOs include VASs (Visual Analog Scales), patient and parent questionnaires examining HRQOL in patients, and composite scores such as the JADAS (Juvenile Arthritis Disease Activity Score), which incorporates physician and patient/parent assessment of disease activity along with more objective data such as number of swollen joints and laboratory values (ESR or CRP) to determine a disease activity score [41].

Prognosis

Prognosis for children with JIA depends on the subtype of JIA as well as how long the child has had active disease. The myth that children will "grow out of it" has been largely refuted, with the majority of children either continuing to have disease into adulthood or suffering sequelae of undertreated or long-standing disease. Persistent oligoarticular JIA is associated with the best prognosis, and several studies reveal that over half of these patients experience long-lasting remission into adulthood. In a systematic review evaluating the frequency of remission among JIA subtypes, persistent oligoarticular JIA had a 66% chance of being in remission at a median of 9 years out from disease, whereas patients with RF+ polyarticular JIA and the ERA subtype had the least chance of attaining remission [64]. In a 30-year follow-up study of patients with JIA, 41% still had active disease into adulthood. The remission rate for persistent oligoarticular was 80%, and about half of the patients with extended disease or RF- polyarticular disease were in remission at this time [65].

Children with JIA report a lower health-related quality of life (HRQOL) compared to their healthy peers, particularly in children with polyarticular JIA, extended oligoarticular JIA, and systemic JIA. Fatigue is a major complaint in these children and has been found to be directly related to disease activity [66]. Physical function is another domain that is affected. In a large, multinational, multicenter, cross-sectional study, HRQOL was assessed in 6639 patients, of whom 3324 had JIA. The same three aforementioned subtypes were most affected, and persistent oligoarticular JIA was least affected. The most significant impairment noted in these children were in the physical domain, including both functionality affecting physical well-being and the degree of pain affecting psychosocial well-being [67]. Several studies suggest that the ERA subtype is associated with worse pain and function, compared to the other subtypes [68]. Fortunately, over the past decade, there has been a pronounced improvement in functional disability in patients with JIA, likely reflective of the improved treatments that are now available [62]. For patients with low HRQOL, psychological intervention has been beneficial, including guided self-reflection [69].

Summary

JIA is the most chronic disease of childhood and is characterized by synovial inflammation. There are several subtypes which are defined according to the number of joints involved, extra-articular symptoms, and family history. MRI and MSUS have emerged as the imaging modalities of choice in JIA, being able to evaluate for active as well as chronic disease. There have been significant advances in the understanding and treatment of JIA. The introduction of biologics revolutionized the way we treat JIA, resulting in substantial improvement in the quality of life of our patients. As we continue to learn more about the underlying genetics and epigenetics and how these factors influence immune-pathogenesis, treatments will become increasingly more targeted and effective. Biomarkers are being developed in RA and JIA with the ultimate hope of achieving personalized medicine where it would be possible determine subtype, optimal therapy and prognosis at the initial diagnosis of JIA. Incorporating early diagnosis with a multidisciplinary approach to treatment will hopefully minimize disease activity and maximize physical function and quality of life in patients with JIA.

Clinical Pearls

- Juvenile Idiopathic Arthritis (JIA) is a clinically heterogeneous group of diseases characterized by arthritis that begins before the age of 16, lasts at least 6 weeks, and has no other identifiable cause [2]. There are seven different subtypes of JIA

which are classified according to the number and distribution of joints involved, as well as extra-articular symptoms, labs, and family history.
- JIA is an autoimmune disease whose pathogenesis is influenced by genetic, epigenetic, and environmental factors.
- Arthritis is a **clinical** diagnosis, based on history and physical examination. Labs are not helpful in diagnosing arthritis, they are only helpful in determining JIA subtype.
- Uveitis is present in up to 20% patients with JIA. Risk factors include ANA positivity, younger age of onset, female sex and having oligoarticular JIA.
- Ultrasound and MRI are the imaging modalities of choice for evaluating disease activity in JIA. Radiographs are best used to evaluate for signs of chronic disease.
- Most patients with JIA do not achieve life-long remission and require long-term treatment. However, early aggressive therapy leads to better outcomes and less disease-related morbidity in children with JIA.

References

1. Harrold LR, Salman C, Shoor S, Curtis JR, Asgari MM, Gelfand JM, et al. Incidence and prevalence of juvenile idiopathic arthritis among children in a managed care population, 1996-2009. J Rheumatol. 2013;40(7):1218–25.
2. Petty RE, Southwood TR, Manners P, Baum J, Glass DN, Goldenberg J, et al. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. J Rheumatol. 2004;31(2):390–2.
3. Martini A, Ravelli I, Beresford MW, Burgos-Vargas R, Cuttica R, Ilowite NT, et al. Toward new classification criteria for juvenile idiopathic arthritis: first steps, pediatric rheumatology international trials organization international consensus. J Rheumatol. 2018;45:8.
4. Beresford MW. Juvenile idiopathic arthritis: new insights into classification, measures of outcome, and pharmacotherapy. Paediatr Drugs. 2011;13(3):161–73.
5. Hinks A, Marion MC, Cobb J, Comeau ME, Sudman M, Ainsworth HC, et al. Brief report: the genetic profile of rheumatoid factor-positive polyarticular juvenile idiopathic arthritis resembles that of adult rheumatoid arthritis. Arthritis Rheumatol. 2018;70(6):957–62.
6. Colbert RA. Classification of juvenile spondyloarthritis: enthesitis-related arthritis and beyond. Nat Rev Rheumatol. 2010;6(8):477–85.
7. Ombrello MJ, Arthur VL, Remmers EF, Hinks A, Tachmazidou I, Grom AA, et al. Genetic architecture distinguishes systemic juvenile idiopathic arthritis from other forms of juvenile idiopathic arthritis: clinical and therapeutic implications. Ann Rheum Dis. 2017;76(5):906–13.
8. Cimaz R. Systemic-onset juvenile idiopathic arthritis. Autoimmun Rev. 2016;15(9):931–4.
9. Nordal E, Zak M, Aalto K, Berntson L, Fasth A, Herlin T, et al. Ongoing disease activity and changing categories in a long-term nordic cohort study of juvenile idiopathic arthritis. Arthritis Rheum. 2011;63(9):2809–18.
10. Mo A, Marigorta UM, Arafat D, Chan LHK, Ponder L, Jang SR, et al. Disease-specific regulation of gene expression in a comparative analysis of juvenile idiopathic arthritis and inflammatory bowel disease. Genome Med. 2018;10(1):48.
11. Hersh AO, Prahalad S. Immunogenetics of juvenile idiopathic arthritis: a comprehensive review. J Autoimmun. 2015;64:113–24.
12. Cobb JE, Hinks A, Thomson W. The genetics of juvenile idiopathic arthritis: current understanding and future prospects. Rheumatology (Oxford). 2014;53(4):592–9.

13. Funk RS, Chan MA, Becker ML. Cytokine biomarkers of disease activity and therapeutic response after initiating methotrexate therapy in patients with juvenile idiopathic arthritis. Pharmacotherapy. 2017;37(6):700–11.
14. van Loosdregt J, van Wijk F, Prakken B, Vastert B. Update on research and clinical translation on specific clinical areas from biology to bedside: unpacking the mysteries of juvenile idiopathic arthritis pathogenesis. Best Pract Res Clin Rheumatol. 2017;31(4):460–75.
15. Gowdie PJ, Tse SM. Juvenile idiopathic arthritis. Pediatr Clin N Am. 2012;59(2):301–27.
16. Greenwald AG, Zakerzadeh A, Laxer RM, Schneider R, Cameron B, Feldman B, et al. Later-onset rheumatoid factor negative polyarticular juvenile idiopathic arthritis (JIA): a unique patient group? Clin Exp Rheumatol. 2013;31(4):645–52.
17. Stoll ML, Amin D, Powell KK, Poholek CH, Strait RH, Aban I, et al. Risk factors for intraarticular heterotopic bone formation in the temporomandibular joint in juvenile idiopathic arthritis. J Rheumatol. 2018;45(9):1301–7.
18. Stoll ML, Kau CH, Waite PD, Cron RQ. Temporomandibular joint arthritis in juvenile idiopathic arthritis, now what? Pediatr Rheumatol Online J. 2018;16(1):32. https://doi.org/10.1186/s12969-018-0244-y.
19. Weiss PF, Arabshahi B, Johnson A, Bilaniuk LT, Zarnow D, Cahill AM, Feudtner C, Cron RQ. High prevalence of temporomandibular joint arthritis at disease onset in children with juvenile idiopathic arthritis, as detected by magnetic resonance imaging but not by ultrasound. Arthritis Rheum. 2008;58(4):1189–96.
20. Ravelli A, Martini A. Juvenile idiopathic arthritis. Lancet. 2007;369(9563):767–78.
21. Zisman D, Stoll ML, Butbul Aviel Y, Mellins ED. Juvenile psoriatic arthritis: a report from the GRAPPA 2017 annual meeting. J Rheumatol Suppl. 2018;94:11–6.
22. Zisman D, Gladman DD, Stoll ML, Strand V, Lavi I, Hsu JJ, et al. The juvenile psoriatic arthritis cohort in the CARRA registry: clinical characteristics, classification, and outcomes. J Rheumatol. 2017;44:342–51.
23. Samad A, Stoll ML, Lavi I, Hsu J, Strand V, Robinson TN, et al. Adiposity in juvenile psoriatic arthritis. J Rheumatol. 2018;45:411–8.
24. Taylor-Gjevre RM, Nair B, Gjevre J, Leswick D. Trauma and psoriatic arthritis: is there a relationship? Can Fam Physician. 2012;58(11):e636–40.
25. Hsieh J, Kadavath S, Efthimiou P. Can traumatic injury trigger psoriatic arthritis? A review of the literature. Clin Rheumatol. 2014;33(5):601–8.
26. Horneff G, Schulz AC, Klotsche J, Hospach A, Minden K, Foeldvari I, et al. Experience with etanercept, tocilizumab and interleukin-1 inhibitors in systemic onset juvenile idiopathic arthritis patients from the BIKER registry. Arthritis Res Ther. 2017;19(1):256.
27. Janow G, Schanberg LE, Setoguchi S, Hasselblad V, Mellins ED, Schneider R, et al. The systemic juvenile idiopathic arthritis cohort of the childhood arthritis and rheumatology research alliance registry: 2010-2013. J Rheumatol. 2016;43(9):1755–62.
28. Hugle B, Hinze C, Lainka E, Fischer N, Haas JP. Development of positive antinuclear antibodies and rheumatoid factor in systemic juvenile idiopathic arthritis points toward an autoimmune phenotype later in the disease course. Pediatr Rheumatol Online J. 2014;12:28.
29. Vastert SJ, Prakken BJ. Paediatric rheumatic disease: diagnosing macrophage activation syndrome in systemic JIA. Nat Rev Rheumatol. 2014;10(11):640–2.
30. Lerkvaleekul B, Vilaiyuk S. Macrophage activation syndrome: early diagnosis is key. Open Access Rheumatol. 2018;10:117–28.
31. Sen ES, Ramanan AV. Juvenile idiopathic arthritis-associated uveitis. Best Pract Res Clin Rheumatol. 2017;31(4):517–34.
32. Heiligenhaus A, Niewerth M, Ganser G, Heinz C, Minden K, German Uveitis in Childhood Study G. Prevalence and complications of uveitis in juvenile idiopathic arthritis in a population-based nation-wide study in Germany: suggested modification of the current screening guidelines. Rheumatology (Oxford). 2007;46(6):1015–9.

33. Tugal-Tutkun I, Quartier P, Bodaghi B. Disease of the year: juvenile idiopathic arthritis-associated uveitis—classification and diagnostic approach. Ocul Immunol Inflamm. 2014;22(1):56–63.
34. Weiss PF. Update on enthesitis-related arthritis. Curr Opin Rheumatol. 2016;28(5):530–6.
35. Ikeda K, Nakagomi D, Sanayama Y, Yamagata M, Okubo A, Iwamoto T, et al. Correlation of radiographic progression with the cumulative activity of synovitis estimated by power Doppler ultrasound in rheumatoid arthritis: difference between patients treated with methotrexate and those treated with biological agents. J Rheumatol. 2013;40(12):1967–76.
36. Bugni Miotto e Silva V, de Freitas Tavares da Silva C, de Aguiar Vilela Mitraud S, Nely Vilar Furtado R, Esteves Hilario MO, Natour J, et al. Do patients with juvenile idiopathic arthritis in remission exhibit active synovitis on joint ultrasound? Rheumatol Int 2014;34(7):937–945.
37. Collado P, Gamir ML, Lopez-Robledillo JC, Merino R, Modesto C, Monteagudo I. Detection of synovitis by ultrasonography in clinically inactive juvenile idiopathic arthritis on and off medication. Clin Exp Rheumatol. 2014;32(4):597–603.
38. Nguyen H, Ruyssen-Witrand A, Gandjbakhch F, Constantin A, Foltz V, Cantagrel A. Prevalence of ultrasound-detected residual synovitis and risk of relapse and structural progression in rheumatoid arthritis patients in clinical remission: a systematic review and meta-analysis. Rheumatology (Oxford). 2014;53(11):2110–8.
39. Sibbitt WL Jr, Band PA, Kettwich LG, Chavez-Chiang NR, Delea SL, Bankhurst AD. A randomized controlled trial evaluating the cost-effectiveness of sonographic guidance for intra-articular injection of the osteoarthritic knee. J Clin Rheumatol. 2011;17(8):409–15.
40. Young CM, Shiels WE 2nd, Coley BD, Hogan MJ, Murakami JW, Jones K, et al. Ultrasound-guided corticosteroid injection therapy for juvenile idiopathic arthritis: 12-year care experience. Pediatr Radiol. 2012;42(12):1481–9.
41. Giancane G, Consolaro A, Lanni S, Davi S, Schiappapietra B, Ravelli A. Juvenile idiopathic arthritis: diagnosis and treatment. Rheumatol Ther. 2016;3(2):187–207.
42. Poddubnyy D, Rudwaleit M, Haibel H, Listing J, Marker-Hermann E, Zeidler H, et al. Effect of non-steroidal anti-inflammatory drugs on radiographic spinal progression in patients with axial spondyloarthritis: results from the German Spondyloarthritis Inception Cohort. Ann Rheum Dis. 2012;71(10):1616–22.
43. Weiss PF, Colbert RA. Juvenile spondyloarthritis: a distinct form of juvenile arthritis. Pediatr Clin N Am. 2018;65(4):675–90.
44. Ravelli A, Lattanzi B, Consolaro A, Martini A. Glucocorticoids in paediatric rheumatology. Clin Exp Rheumatol. 2011;29(5 Suppl 68):S148–52.
45. Sherry DD, Stein LD, Reed AM, Schanberg LE, Kredich DW. Prevention of leg length discrepancy in young children with pauciarticular juvenile rheumatoid arthritis by treatment with intraarticular steroids. Arthritis Rheum. 1999;42(11):2330–4.
46. Scott C, Meiorin S, Filocamo G, Lanni S, Valle M, Martinoli C, et al. A reappraisal of intra-articular corticosteroid therapy in juvenile idiopathic arthritis. Clin Exp Rheumatol. 2010;28(5):774–81.
47. Braun J. Methotrexate: optimizing the efficacy in rheumatoid arthritis. Ther Adv Musculoskelet Dis. 2011;3(3):151–8.
48. Beukelman T, Patkar NM, Saag KG, Tolleson-Rinehart S, Cron RQ, DeWitt EM, et al. American College of Rheumatology recommendations for the treatment of juvenile idiopathic arthritis: initiation and safety monitoring of therapeutic agents for the treatment of arthritis and systemic features. Arthritis Care Res (Hoboken). 2011;63(4):465–82.
49. Casanova Sorni C, Roma Sanchez E, Pelufo Pellicer A, Poveda Andres JL. [Leflunomide: assessing teratogenic risk during the first trimester of pregnancy]. Farm Hosp 2005;29(4):265–8.
50. Amarilyo G, Tarp S, Foeldvari I, Cohen N, Pope TD, Woo JM, et al. Biological agents in polyarticular juvenile idiopathic arthritis: a meta-analysis of randomized withdrawal trials. Semin Arthritis Rheum. 2016;46(3):312–8.

51. Beukelman T, Xie F, Chen L, Horton DB, Lewis JD, Mamtani R, et al. Risk of malignancy associated with paediatric use of tumour necrosis factor inhibitors. Ann Rheum Dis. 2018;77(7):1012–6.
52. Gorman JD, Sack KE, Davis JC Jr. Treatment of ankylosing spondylitis by inhibition of tumor necrosis factor alpha. N Engl J Med. 2002;346(18):1349–56.
53. Horneff G, De Bock F, Foeldvari I, Girschick HJ, Michels H, Moebius D, et al. Safety and efficacy of combination of etanercept and methotrexate compared to treatment with etanercept only in patients with juvenile idiopathic arthritis (JIA): preliminary data from the German JIA Registry. Ann Rheum Dis. 2009;68(4):519–25.
54. Wallace CA, Giannini EH, Spalding SJ, Hashkes PJ, O'Neil KM, Zeft AS, et al. Clinically inactive disease in a cohort of children with new-onset polyarticular juvenile idiopathic arthritis treated with early aggressive therapy: time to achievement, total duration, and predictors. J Rheumatol. 2014;41(6):1163–70.
55. Stoll ML, Cron RQ. Treatment of juvenile idiopathic arthritis: a revolution in care. Pediatr Rheumatol Online J. 2014;12:13.
56. Picchianti Diamanti A, Rosado MM, Scarsella M, Germano V, Giorda E, Cascioli S, et al. Abatacept (cytotoxic T lymphocyte antigen 4-immunoglobulin) improves B cell function and regulatory T cell inhibitory capacity in rheumatoid arthritis patients non-responding to anti-tumour necrosis factor-alpha agents. Clin Exp Immunol. 2014;177(3):630–40.
57. Ruperto N, Brunner HI, Zuber Z, Tzaribachev N, Kingsbury DJ, Foeldvari I, et al. Pharmacokinetic and safety profile of tofacitinib in children with polyarticular course juvenile idiopathic arthritis: results of a phase 1, open-label, multicenter study. Pediatr Rheumatol Online J. 2017;15(1):86.
58. Schulze-Koops H, Skapenko A. Biosimilars in rheumatology: a review of the evidence and their place in the treatment algorithm. Rheumatology (Oxford). 2017;56(suppl_4):iv30–48.
59. Stoll ML, Cron RQ. Treatment of juvenile idiopathic arthritis in the biologic age. Rheum Dis Clin N Am. 2013;39(4):751–66.
60. Giannini EH, Ilowite NT, Lovell DJ, Wallace CA, Rabinovich CE, Reiff A, et al. Long-term safety and effectiveness of etanercept in children with selected categories of juvenile idiopathic arthritis. Arthritis Rheum. 2009;60(9):2794–804.
61. Nigrovic PA, Mannion M, Prince FH, Zeft A, Rabinovich CE, van Rossum MA, et al. Anakinra as first-line disease-modifying therapy in systemic juvenile idiopathic arthritis: report of forty-six patients from an international multicenter series. Arthritis Rheum. 2011;63(2):545–55.
62. Minden K. Adult outcomes of patients with juvenile idiopathic arthritis. Horm Res. 2009;72(Suppl 1):20–5.
63. Anink J, Prince FH, Dijkstra M, Otten MH, Twilt M, ten Cate R, et al. Long-term quality of life and functional outcome of patients with juvenile idiopathic arthritis in the biologic era: a longitudinal follow-up study in the Dutch Arthritis and Biologicals in Children Register. Rheumatology (Oxford). 2015;54(11):1964–9.
64. Shoop-Worrall SJW, Kearsley-Fleet L, Thomson W, Verstappen SMM, Hyrich KL. How common is remission in juvenile idiopathic arthritis: a systematic review. Semin Arthritis Rheum. 2017;47(3):331–7.
65. Selvaag AM, Aulie HA, Lilleby V, Flato B. Disease progression into adulthood and predictors of long-term active disease in juvenile idiopathic arthritis. Ann Rheum Dis. 2016;75(1):190–5.
66. Ringold S, Wallace CA, Rivara FP. Health-related quality of life, physical function, fatigue, and disease activity in children with established polyarticular juvenile idiopathic arthritis. J Rheumatol. 2009;36(6):1330–6.
67. Oliveira S, Ravelli A, Pistorio A, Castell E, Malattia C, Prieur AM, et al. Proxy-reported health-related quality of life of patients with juvenile idiopathic arthritis: the Pediatric Rheumatology International Trials Organization multinational quality of life cohort study. Arthritis Rheum. 2007;57(1):35–43.

68. Weiss PF, Beukelman T, Schanberg LE, Kimura Y, Colbert RA, Investigators CR. Enthesitis-related arthritis is associated with higher pain intensity and poorer health status in comparison with other categories of juvenile idiopathic arthritis: the Childhood Arthritis and Rheumatology Research Alliance Registry. J Rheumatol. 2012;39(12):2341–51.
69. Fuchs CE, Van Geelen SM, Hermans HJ, Van De Putte EM, Van Geel R, Sinnema G, et al. Psychological intervention for adolescents with juvenile idiopathic arthritis: for whom and when? J Rheumatol. 2013;40(4):528–34.

Chapter 27
Septic Arthritis

Suzanne Amaro

Overview

Septic arthritis (SA), also known as septic joint or infectious arthritis, is the presence of microorganisms in joint space. Septic arthritis often presents with pain in only one joint space; 90% of cases are monoarticular [1]. In children, lower extremity SA typically presents with the inability to bear weight on the affected limb as well as limiting the range of motion due to pain and swelling. The infection causes synovitis of the affected joint resulting in pain. Larger joints are most commonly affected including the shoulder, hip, and knee but SA may occur in any joint.

Various microorganisms may be responsible for septic arthritis, including bacteria, fungi, mycobacteria, and viruses. Bacteria continue to be the most commonly found pathogen, specifically Staphylococcus aureus. In the United States, staphylococcus aureus is the most common etiological agent in all septic arthritis cases [2]. Infections that are bacterial in nature are classified as gonococcal or nongonococcal.

Epidemiology

Microorganisms can be introduced by a penetrating injury, which can arise from nearby inoculated soft tissue or via the bloodstream. The free-floating bacteria then travel through the body, landing in a joint space. The incidence of bacterial arthritis

S. Amaro (✉)
Department of Orthopaedic Surgery, Ann & Robert H. Lurie Children's Hospital, Chicago, IL, USA
e-mail: samaro@luriechildrens.org

J. F. Sarwark, R. L. Carl (eds.), *Orthopaedics for the Newborn and Young Child*,
https://doi.org/10.1007/978-3-031-11136-5_27

in children ranges from 1 to 37 cases per 100,000 people [3]. Children younger than 3 years are affected most frequently. Boys are affected two more times than girls [3]. Risk factors include children less than 3 years of age, male gender, preceding trauma, immunodeficiency, and recent umbilical artery catheterization in the neonate.

Common Clinical Presentation

A thorough history is crucial to rule out a differential diagnosis. It is important to differentiate between acute joint infections versus possible chronic rheumatologic processes versus transient synovitis. Septic arthritis generally presents with acute onset of joint pain, fever, gait disturbance, joint swelling, and erythema. Some children may present with irritability and malaise. Additional symptoms commonly reported in infants and neonates include refusal to eat, irritability, and crying during movement. Children may or may not present with a fever. Joint swelling may not be noticeable in infants with more subcutaneous fat. Occasionally a preceding fall or injury is reported, although the injury is not always known. A small bump on the knee, a twisted ankle, or overuse of a shoulder causes the body to begin leukocyte extravasation. The extra fluid and leukocytes migrate to the area of injury to begin the healing process. If there are bacteria present in the surrounding tissues or blood, the joint will inevitably become infected due to the increased blood flow which allows bacteria to enter the space at an alarming rate. The epiphyseal plate in older children prevents infection from entering the joint space from nearby bone; however, neonates and younger children less than 18 months of age have transphyseal blood vessel communication, which can lead to the spread of infection from metaphysis to the joint. 60–100% of neonates with septic arthritis have adjacent osteomyelitis [4]. Children found to have Kingella kingae on bacterial culture results, usually have a preceding upper respiratory tract infection since Kingella colonizes the oropharynx in children.

Transient synovitis is a benign condition characterized by acute hip pain associated joint effusion. The cause is generally unknown although most affected children are between 3 and 9 years of age. The majority of children with transient synovitis have a recent upper respiratory infection or other viral illness. Patients complain of hip pain, pain with weight bearing and plus or minus low-grade fever but appear well despite symptoms. The duration of symptoms is typically 3–5 days. Workup is not needed in well-appearing children ages 3–9 years with clinical findings suggestive of transient synovitis. Treatment involves nonsteroidal anti-inflammatory medication to help with discomfort.

In the adolescent population, it is important to ask about sexual history, due to the risk of gonococcal infection. Disseminated gonococcal infection is a rare complication of gonorrhea, arising in 0.5–3% of cases [5]. Patients usually report

monoarticular or asymmetric polyarticular joint pain involving the knee(s), wrist(s), ankle(s), and elbow(s). Skin lesions are present in 75% of cases [5]. Patients may also complain of pelvic pain, vaginal discharge, sore throat, and/or cervical lymphadenopathy. Testing should include blood cultures, urethral cultures in males, and cervical cultures in females if gonococcal infection is suspected.

Lyme disease should also be considered as a possible etiology of septic arthritis. A history of camping in endemic areas or tick bites increases the probably of Lyme disease.

On physical examination, every joint should be assessed to rule out generalized joint erythema, swelling, or tenderness. Infected joints are generally swollen, signaling effusion. They are sometimes erythematous, warm to the touch, and tender although deep joints, such as the hip, may not exhibit the same symptomatology. Limited range of motion is almost always present secondary to pain and effusion. Patients with septic arthritis involving the hip often feel more comfortable holding the affected hip in a flexed, abducted, and externally rotated position. Pain may also be referred to groin, thigh, or knee. Patients with septic arthritis present with monoarticular symptoms versus patients with rheumatologic disease who often present with more than one affected joint. Polyarticular arthritis may also be found in gonococcal septic arthritis therefore clinicians should always assess for fever, rash, limited range of motion, warmth, tenderness, swelling, joint effusion, and impaired gait in all patients.

Evaluation

Bacterial arthritis usually has a rapidly progressive course with a high likelihood of joint damage. For this reason, evaluation and treatment should be initiated quickly.

Laboratory tests are easily obtained and can be helpful in identifying an infectious or inflammatory process. Inflammatory markers including erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are helpful in identifying an acute process. However, they do not differentiate between septic and inflammatory arthritis [3]. A CBC or complete blood count may also be useful in assessing leukocytosis which can indicate an acute infectious process.

The Kocher criteria were developed to differentiate between septic arthritis and transient synovitis in young children. These criteria include four clinical and laboratory testing findings including elevated white blood cell (WBC) count, elevated erythrocyte sedimentation rate (ESR), refusal to bear weight on the affected extremity, and fever. In the absence of all four criteria, septic arthritis is fairly unlikely. With each additional criterium that is present, the risk of septic arthritis increases [6]. A history of a prior visit to a health care provider has also been shown to increase the likelihood of septic arthritis [7] (Table 27.1).

Table 27.1 Kocher Criteria [6]

Symptoms	Value
Non-weight bearing Fever greater than 38.5 °C. WBC greater than 12,000 ESR greater than 40 mm/h	0 symptoms = <0.2% 1 symptom = 10% 2 symptoms = 35% 3 symptoms = 75% 4 symptoms= >99%

If bacterial arthritis is suspected, evaluation should include aspiration of the affected joint. Synovial fluid should be sent for lab analysis including cell count, bacterial culture, and gram stain. Uninfected joint fluid is clear and colorless. Infected joint fluid is usually yellow, green, or tan in color and is more opaque due to the presence of microorganisms as well as excess white blood cells. Cell count analysis reveals a white blood cell count above 50,000 cells/mcL with polymorphonuclear cells greater than 75% [3] is considered indicative of infection. The cell count may take a few hours to obtain, and the results of bacterial cultures may take several days; if there is clinical suspicion of bacterial arthritis, treatment should not be delayed pending the results of these tests. The bacterial culture is helpful in narrowing antibiotic coverage. Joint aspiration should always occur under the most sterile conditions. It is possible to introduce bacteria into the joint if completed in an unsterile environment. Blood cultures should also be sent for analysis to rule out septicemia which can be life-threatening. Approximately 20% of patients will have a positive blood culture [1]. Clinicians should be aware that if a patient has received antibiotics recently, bacterial culture may yield a false negative result.

Imaging studies are most useful for assessing joint effusion as well as abnormalities in the bone such as osteomyelitis or fracture. Ultrasound is helpful in diagnosing joint effusions that are not apparent on a physical exam. Magnetic resonance imaging (MRI) allows for the detection of abnormalities in soft tissue, bone, and cartilage. Obtaining an MRI may detect osteomyelitis or an abscess, as well as possible joint effusions. MRI has some downfalls such as a high cost and the possible need for sedation based on the patient's age or tolerance. If an infection is suspected, MRI should also be obtained with and without contrast. MRI is not typically warranted when joint aspiration results indicated likely septic arthritis; however, if a patient is not responding to treatment within 48 h then an MRI should be considered [3] (Figs. 27.1, 27.2, 27.3, and 27.4).

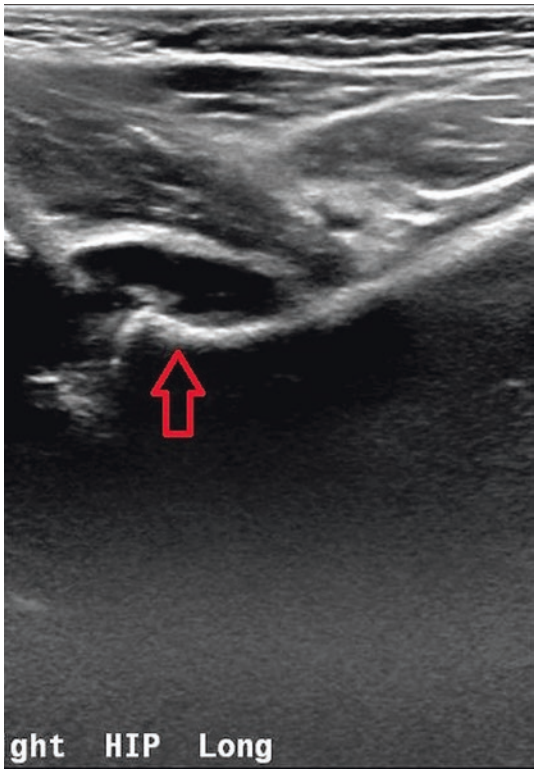


Fig. 27.1 Ultrasound of hip revealing joint effusion

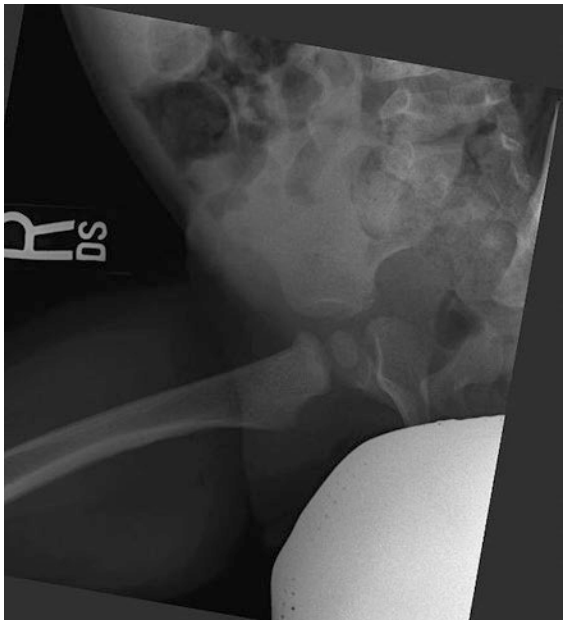


Fig. 27.2 X-ray of same right hip showing no osseous abnormality although the patient was noted to have osteomyelitis and joint effusion on MRI

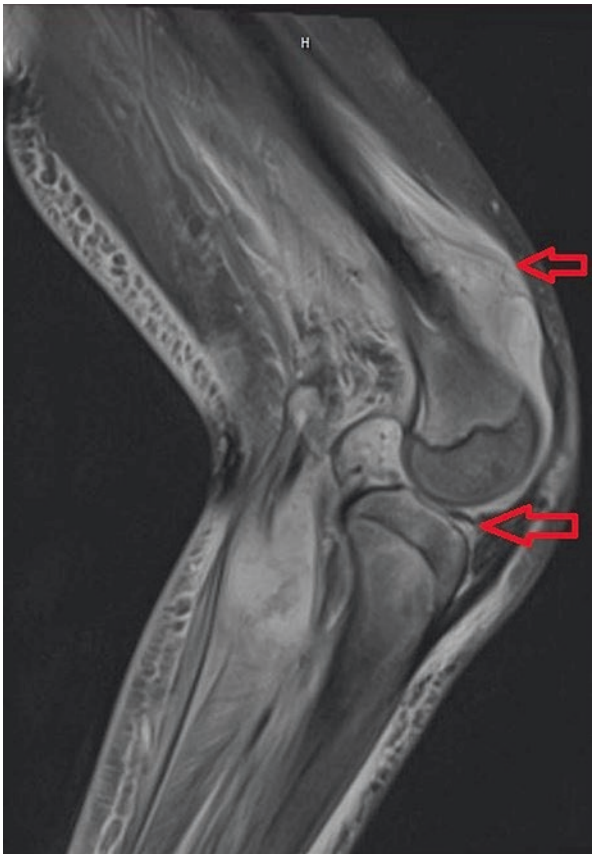


Fig. 27.3 MRI of knee revealing large complex joint effusion. An abscess is also noted superior to the knee joint within the vastus medialis that appears to extend into the joint space

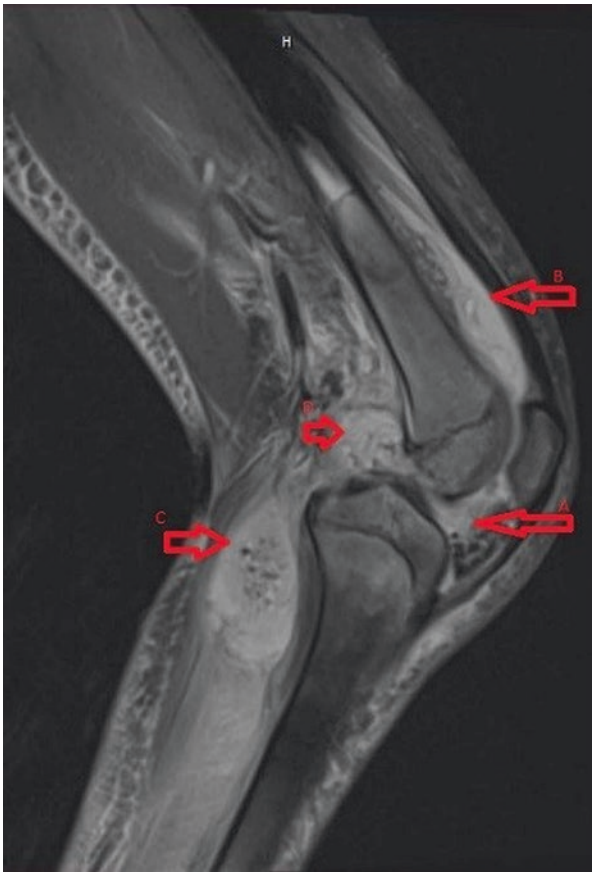


Fig. 27.4 (**a**) MRI of knee revealing large complex joint effusion. (**b**) An abscess is also noted superior to the knee joint within the vastus medialis that appears to extend into the joint space. (**c**) An irregular-shaped abscess is noted in the posterior calf musculature posterior to the tibia. (**d**) Abscess extends from vastus medialis into the joint space, into the posterior knee, ending at the proximal calf

Treatment/Management

Prompt treatment is crucial to minimizing complications and effectively treating septic arthritis. Delay in treatment may result in complications which may include joint degradation and ischemia leading to chronic inflammation and destruction of blood vessels, cartilage, and the joint capsule. The release of proteolytic enzymes from inflammatory and synovial cells, cartilage, and bacteria may cause articular surface damage within 8 h [8]. Septic arthritis of the hip is an emergency and urgent surgical intervention that should be considered [8]. Infection of the hip may cause an increase in joint pressure which may lead to femoral head osteonecrosis if not relieved promptly [6]. Antibiotic treatment is guided by the microorganism identified and should include a multidisciplinary approach. Typically, a pediatric infectious disease specialist manages antibiotic coverage and an orthopedic surgeon evaluates the need for surgical intervention and monitors clinical improvement. An interventional radiologist may be involved in the aspiration of the affected joint.

Empiric antibiotic therapy should be initiated after aspiration without delay. Antibiotics should cover the most prevalent organisms such as Staphylococcus aureus and tailored according to bacterial culture results. Neonates are at the greatest risk for Group Beta Streptococcus and Staphylococcus aureus [3]. Patients who do not improve on antibiotic therapy or who have abscess formation are candidates for surgical drainage. Infants and children with septic arthritis involving the hip typically require incision and drainage due to the risk of damage to the femoral head and subsequent avascular necrosis. Treatment generally includes 2–7 days of intravenous antibiotics followed by 2–4 weeks of oral therapy [3]. Clinical improvement should guide decision-making about the transition to oral antibiotics. Immobilization is not needed and health care providers should encourage movement based on patient comfort.

Staphylococcus aureus is a gram-positive bacteria that is responsible for various severe and life-threatening infections. Methicillin-resistant staphylococcus aureus (MRSA) is responsible for an increasing proportion of staphylococcal infections; however, methicillin-susceptible staph aureus continues to be the leading cause of septic arthritis in children [9]. MRSA is the leading cause of septic arthritis in adults [2]. Antibiotic coverage for stable patients without bacteremia often includes IV clindamycin with transition to oral clindamycin when appropriate [3]. In patients with positive blood cultures, IV vancomycin may be initiated. In children 3 months or older with suspected MSSA infection, IV cefazolin or another first-generation cephalosporin is considered first-line treatment for septic arthritis [3]. If infants are less than 3 months, health care providers should consider adding gentamicin to cover gram-negative organisms until final bacterial cultures return [3].

Kingella kingae is the second most common cause of septic arthritis [10]. In a study by Illan-Ramos et al. using polymerase chain reaction (PCR) to increase the sensitivity of testing, K. kingae was the most common bacterium causing septic arthritis in children [10]. Kingella is a common colonizer of the oropharynx in children. A first-generation cephalospor.in is the preferred treatment for Kingella infections.

Natural History, Primary and Secondary Prevention

The natural history of septic arthritis starts with susceptibility in the population and identifying risk factors then progresses to exposure of the pathogen resulting in early pathologic change. Primary prevention should focus on hand hygiene and skin care. In the hospital setting, it is important to identify high-risk individuals such as those who are immunocompromised. Secondary prevention has similar foundations as primary prevention however the focus should be on early recognition and treatment of septic arthritis.

References

1. Shirtliff ME, Mader JT. Acute Septic Arthritis. Clin Microbiol Rev. 2002;15(4):527–44.
2. Up To Date. Bacterial arthritis: epidemiology, pathogenesis, and microbiology in infants and children. 2018. http://www.uptodate.com. https://www.uptodate.com/contents/bacterial-arthritis-epidemiology-pathogenesis-and-microbiology-in-infants-and-children?search=Gonococcal%20Arthritis&source=search_result&selectedTitle=3~19&usage_type=default&display_rank=3. Accessed 8 Oct 2018.
3. DynaMed Plus [Internet]. Ipswich (MA): EBSCO Information Services. 1995. Record No. 921096, Septic arthritis in children; [updated 2018 Jun 13, Accessed 12 Oct 2018].
4. Wheeless C. Osteomyelitis in the Infant. Wheeless' Textbook of Orthopaedics. Duke Orthopaedics. 2012. http://www.wheelessonline.com/ortho/osteomyelitis_in_the_infants. Accessed 12 Oct 2018.
5. Hernández-Rupérez MB, Suárez-Arrabal MDC, Villa-García Á, Zarzoso-Fernández S, Navarro-Gómez M, Santos-Sebastián M, et al. Kingella kingae as the main cause of septic arthritis: importance of molecular diagnosis. Pediatr Infect Dis J. 2018;37(12):1211–6.
6. Kocher MS, Zurakowski D, Kasser JR. Differentiating between septic arthritis and transient synovitis of the hip in children: an evidence-based clinical prediction algorithm. J Bone Joint Surg Am. 1999;81(12):1662–70.
7. Luhmann SJ, Jones A, Schootman M, Gordon JE, Schoenecker PL, Luhmann JD. Differentiation between septic arthritis and transient synovitis of the hip in children with clinical prediction algorithms. J Bone Joint Surg Am. 2004;86(5):956–62.
8. DynaMed Plus [Internet]. Ipswich (MA): EBSCO Information Services. 1995. Record No. 921096, Disseminated gonococcal infection; [updated 2010 Jul 08, Accessed 15 Oct 2018].
9. Combs K, Cox K. Clinical outcomes involving patients that develop septic arthritis with methicillin sensitive staphylococcus aureus versus methicillin resistant staphylococcus aureus. J Orthop. 2017;15(1):9–12.
10. Nguyen A, Kan JH, Bisset G, Rosenfield S. Kocher criteria revisited in the era of MRI: how often does the kocher criteria identify underlying osteomyelitis? J Pediatr Orthop. 2017;37(2):e114–9.

Chapter 28
Pediatric Osteomyelitis

David K. Lyons

Brief Overview

Osteomyelitis is an infection of the bone which results in inflammatory destruction of the bone. Infection tends to be located in the metaphysis of long bones. The pediatric population is especially susceptible due to young children's rich metaphyseal blood supply and immature immune system. The most common mechanism is hematogenous spread. Trauma to an extremity and concomitant bacteremia lead to higher susceptibility and seeding of the bone.

Infection is rare in healthy children, but those with certain risk factors or immune compromise are at a higher risk of infection. The most common causative organism is Staphylococcus aureus, but there are several other bacteria that commonly occur in different age groups or in children with certain risk factors.

The chronicity of infection can vary, with acute being most common followed by subacute and chronic. On examination of the child, they may exhibit generalized pain, refusal to bear weight on an affected extremity, limp, swelling, warmth, or tenderness. Fever may or may not be present. Laboratory workup including complete blood count (CBC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and blood or bone cultures are essential in diagnosis and monitoring treatment.

Several imaging modalities are available to help diagnose and monitor infection. Radiographs can help rule out other diagnoses but may not show changes related to acute osteomyelitis until weeks after the initial onset of infection. Magnetic resonance imaging (MRI) with and without contrast is best for early identification and can help evaluate other pathology including surrounding soft tissue infection.

Treatment typically begins with antibiotic therapy. Empiric therapy is begun until cultures can be obtained and the patient can be started on organism-specific antibiotics. The route of administration, as well as duration of antibiotic therapy, are controversial.

D. K. Lyons (✉)
Department of Pediatric Orthopaedics, Ann and Robert Lurie Children's Hospital of Chicago, Chicago, IL, USA

J. F. Sarwark, R. L. Carl (eds.), *Orthopaedics for the Newborn and Young Child*,
https://doi.org/10.1007/978-3-031-11136-5_28

Surgical drainage and debridement may be a necessary adjunct to antibiotic therapy when the patient fails to respond to antibiotic therapy or if there is a significant deep soft tissue or subperiosteal abscess involved. Chronic cases often require surgical intervention as well.

Failure to properly identify or treat osteomyelitis may result in complications such as sepsis, chronic infection, pathologic fracture, or growth disturbance.

Epidemiology

Acute and subacute osteomyelitis affect thousands of children every year. In the United States, the estimated annual incidence is 1 per 5000 children [1, 2]. Osteomyelitis typically affects younger children. Children under age 5 account for half of all cases [3, 4]. Infection in infants younger than 4 months of age is uncommon [5]. Males typically observe higher rates of infection [2].

Acute hematogenous osteomyelitis is uncommon in healthy children. In neonates, factors such as complicated delivery, prematurity, or active maternal infection place the child at higher risk of infection. Children who are immunocompromised, or those with concomitant diseases, such as diabetes, rheumatoid arthritis, chronic renal disease, or hemoglobinopathies, have a higher risk of developing osteomyelitis. Osteomyelitis can be difficult to treat and may result in longer hospital stays for treatment as compared to other musculoskeletal infections.

Pathophysiology

Acute osteomyelitis typically occurs in the metaphysis of long bones. The lower extremities have a higher rate of infection than the upper extremities [6, 7]. The most common cause is hematogenous spread of bacteria. Other causes include direct trauma or invasion from a nearby infection. Hematogenous spread is usually a result of transient bacteremia. An act as benign as brushing one's teeth can release bacteria into the bloodstream or it can originate from local or distant soft tissue infections. Common infections in children such as inner ear infections or pharyngitis can also be the source of this bacteremia [8].

The unique anatomy of pediatric metaphyseal bone places it at risk for infection. In the metaphyseal region, there is sluggish blood flow through the capillaries which allows the bacteria time to colonize this area [9]. The permeability of these capillaries also potentially allows the infiltration of bacteria [10]. A unique feature in the anatomy of newborns is the ability of capillaries to cross from the metaphysis, through the physis, and into the epiphysis [11]. This can lead to the spread of infection into the epiphysis and subsequently the joint [12]. Joint infection can also occur in joints with an intra-articular metaphysis. Joints that include an intra-articular metaphysis are the shoulder, elbow, hip, and ankle. These joints are at risk of developing septic arthritis as osteomyelitis spreads.

Local trauma such as a sprained ankle or direct contusion can precede osteomyelitis. A history of trauma is reported in up to 30% of patients [13, 14]. The cause is thought to be that the local trauma results in increased inflammatory response and vascularity, which in the setting of transient bacteremia, results in the flow of the bacteria to this region [15, 16].

Damage to the bone and surrounding tissues can occur from the bacteria itself but is also related to the body's immune response. Several inflammatory mediators are released during the local immune response, resulting in the activation of osteoclasts, osteoblast necrosis, and vascular insult [17]. This results in bone resorption, also known as osteolysis. Osteolysis can occur with the inactivation or destruction of osteoblasts and activation of osteoclasts.

As the tissues are destroyed and bacteria accumulate, purulent fluid can accrue resulting in abscess formation within the bone. The infection can pass through the cortical bone and result in abscess formation subperiosteally. Abscesses, either subperiosteally or those within the bone, have reduced blood flow making delivery of antibiotic medication to this area difficult.

Chronic cases may arise from ineffective treatment or lack of treatment. Chronic cases result in changes to the bone as a result of the body fighting off the infection. As a result of the local inflammatory reaction, the blood supply can be disrupted resulting in necrosis of the bone. A walled-off area of necrotic bone forms which is called the sequestrum. This necrotic bone can serve as a further nidus for infection. The body's response to this stress is to lay down new bone. A layer of new bone, called the involucrum, surrounds the sequestrum. This may require extensive surgical debridement to help clear the infection.

Microbiology

There are many different bacterial infections which can lead to osteomyelitis. Like many other infections, Staphylococcus aureus remains the most common organism [18]. Infection by different organisms can vary by age groups or certain underlying conditions.

S. aureus is the most common organism found in cases of pediatric osteomyelitis, as well as adult osteomyelitis. Methicillin Sensitive S. Aureus (MSSA) can be treated with several antibiotics; however, Methicillin Resistant S. Aureus (MRSA) can be a much more difficult organism to treat and results in higher rates of complications during treatment. Osteomyelitis caused by MRSA results in an increased risk of thromboembolic events as well as the release of septic emboli [19]. A type of community-acquired MRSA produces a cytotoxin called Panton-Valentine leucocidin (PVL) which can result in more complex infections, prolonged fever, abscesses, DVT, and sepsis [20, 21].

Infections caused by Kingella kingae are increasing. This organism resides in the oropharynx and may spread hematogenously in patients with an upper respiratory infection. Kingella infections are common among children who attend daycare [22]. The increasing rates of infection may be related to the improvements in culturing these bacteria. When culturing an abscess or wound, the clinician needs to specify that the sample is cultured in an enriched blood culture media to evaluate for K. kingae.

Other common organisms include Group B Streptococcus, Pseudomonas, Salmonella, and Haemophilus influenza. Group B strep is common in neonates and newborns as this infection can be picked up from the mother during childbirth. When a child sustains a puncture wound to the foot, especially through a shoe, Pseudomonas may be the causative organism. In children with sickle cell disease, Salmonella may be a specific causative organism. H. influenza was a significant cause of osteomyelitis until the development of its immunization which led to significant decrease in its infection rate.

Clinical Presentation

History and Physical

Diagnosis of osteomyelitis based on history and physical alone can be difficult as this process has similar signs and symptoms as other musculoskeletal infections. The most common symptom is limb pain. This pain may be sudden in onset or gradually increase over several days. If a child is old enough, they may be able to localize pain to a specific limb. In newborns and younger children, it may be more difficult to decipher because they are typically not able to express where it hurts. Parents may note decreased use of an extremity, refusal to crawl, limping, or refusal to bear weight. In the early stages of infection, children may appear well, but as the infection worsens, they may quickly become toxic appearing. A history of fever is nonspecific as nearly half of cases present with no fever [2, 5]. A recent history of trauma may be noted as well. With this list of common symptoms, the differential diagnosis can include osteomyelitis, cellulitis, septic arthritis, inflammatory arthritis, transient synovitis, or tumor. Physical exam, imaging, and laboratory workup can help distinguish osteomyelitis from other musculoskeletal infections.

Physical exam findings can also make osteomyelitis difficult to diagnose in comparison to other infections such as septic arthritis or cellulitis. Inspection of the limb might reveal erythema or edema. Palpation may or may not reveal warmth or tenderness. Tenderness could be either focal or diffuse. A decrease in range of motion may also be noted due to localized pain. Analysis of the child's gait may reveal a limp or refusal to bear weight.

Imaging

Several imaging modalities are available to help evaluate osteomyelitis. MRI or ultrasound may pick up changes acutely, while imaging studies such as x-ray and CT scan may be more useful in the chronic setting or in following the sequelae.

Radiographs are typically the first images obtained. While they may have limited use in diagnosis of the acute setting, they can help rule out other diagnoses including fracture or tumor. Osteomyelitis typically takes time to appear radiographically

since lytic lesions typically do not appear until nearly half of the bone matrix is destroyed (Fig. 28.1). It may take up to 2 weeks before the infection is apparent on an x-ray [23]. Other changes that may be picked up earlier include soft tissue swelling and periosteal elevation or thickening. Chronic infection may lead to radiographic findings such as decreased bone density or visible destruction of bone (Fig. 28.2).

Ultrasound is another readily available imaging modality which may help in diagnosis. Ultrasound can help pick up deep soft tissue swelling or abscesses, the presence of a subperiosteal abscess, and potential destruction of the bone. It can also be used to help guide drainage of these fluid collections for diagnostic and therapeutic purposes (Fig. 28.3).

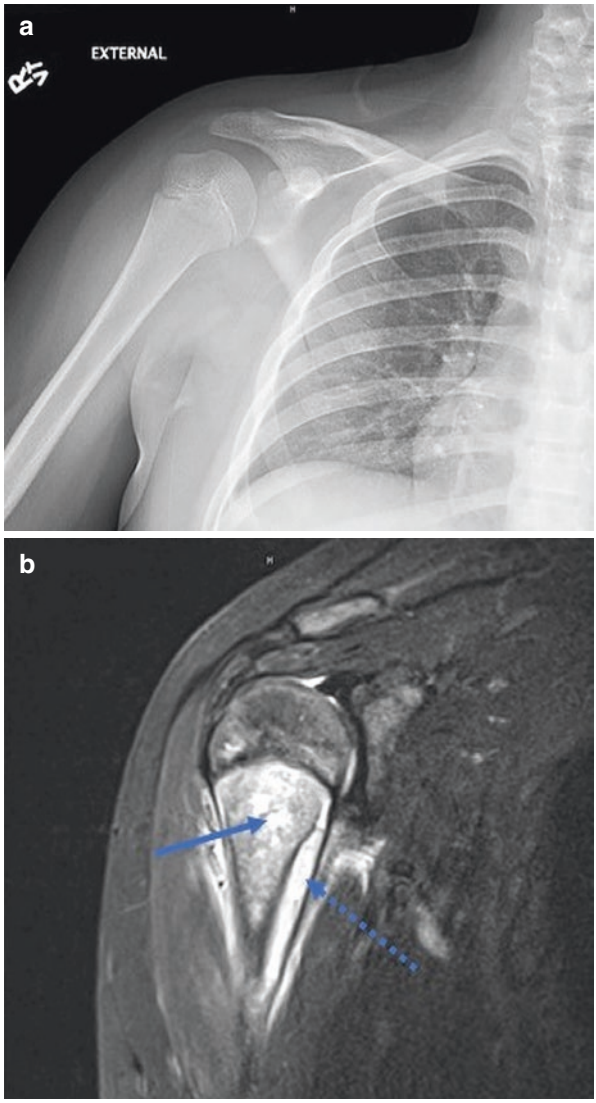


Fig. 28.1 (**a**) Demonstrates a normal appearing shoulder radiograph in a 10-year-old female with 3 days of shoulder pain. (**b**) is an MRI obtained a few hours later in the same patient demonstrating osteomyelitis of the proximal humerus (dotted arrow) as well as a large subperiosteal abscess (solid arrow)

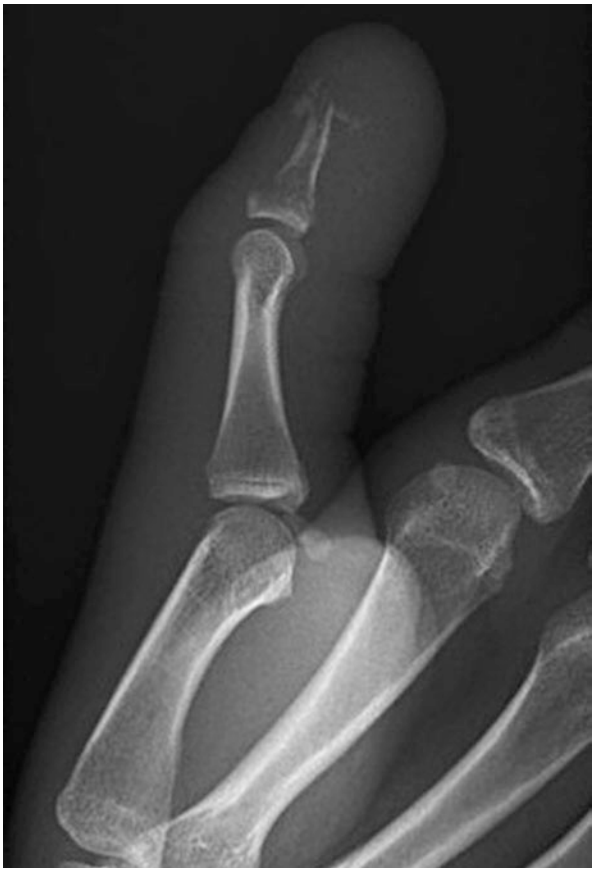


Fig. 28.2 This image demonstrates lytic changes and cortical destruction of the distal phalanx in the thumb of a 17-year-old male with chronic osteomyelitis

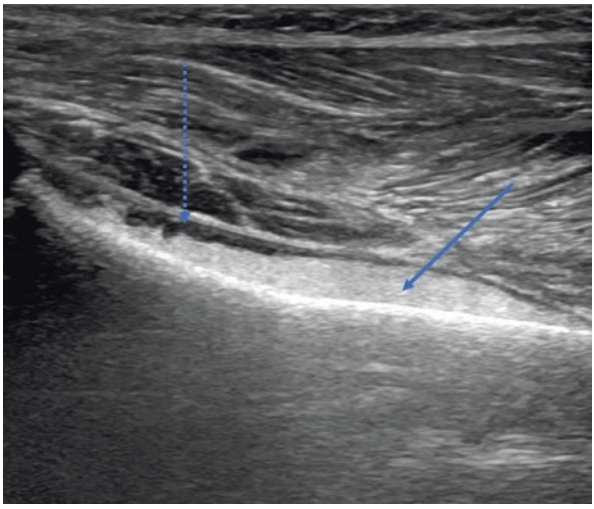


Fig. 28.3 Ultrasound of a 2-year-old male demonstrating subperiosteal abscess. The abscess subsequently aspirated under ultrasound guidance

MRI is the most sensitive imaging modality for the diagnosis of acute osteomyelitis, though it can also be overly sensitive and provide false positives. The MRI will typically show edema within the bone or intramedullary abscess. It can also detect the presence of subperiosteal abscess, intra-articular fluid, or infection in the surrounding soft tissues (Fig. 28.4). Contrast is typically used to increase the sensitivity. Though MRI has several benefits, it is an expensive test and not always readily available. In newborns, sedation is typically required, and recent studies recommend limited anesthesia exposure in newborns.

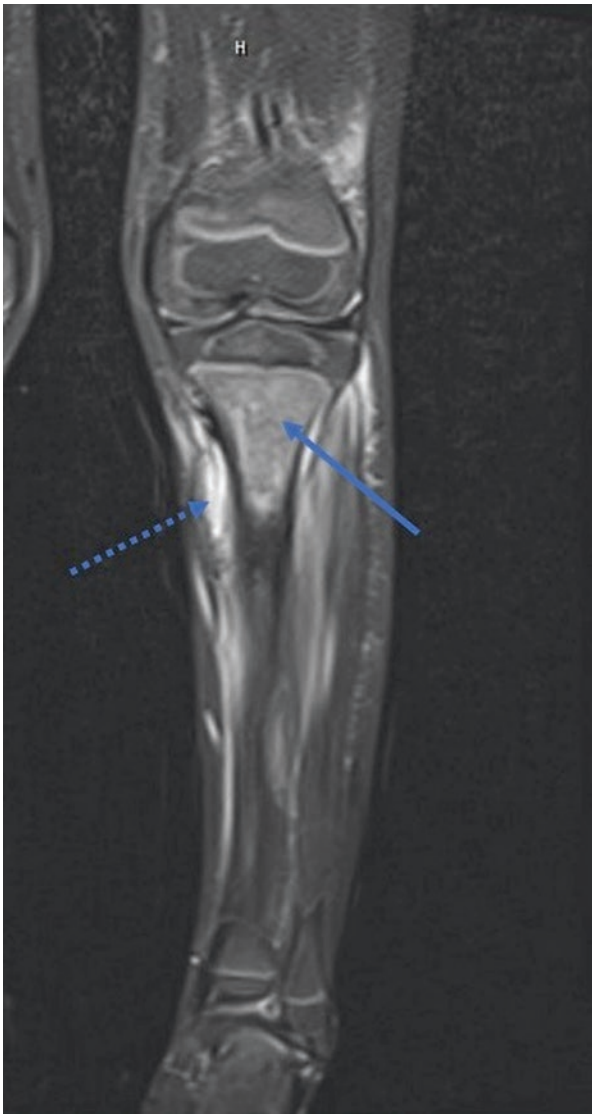


Fig. 28.4 MRI of a 2-year-old male with several days of fevers, leg pain, and inability to bear weight. Changes suggestive of osteomyelitis (solid arrow) as well as subperiosteal abscess (dotted arrow) were noted

Computed tomography can also be used in diagnosis and treatment. The advantages of CT include its availability, lower cost, and decreased need for sedation. Disadvantages include the decreased ability to detect early changes in the bone, difficulty in evaluating surrounding soft tissues, as well as increased radiation exposure in a child. CT scans may better evaluate bony destruction later in the disease course or in chronic cases. This can aid in surgical planning and treatment. CT can also be used to guide needle biopsies or in aspiration of deep abscesses.

Though bone scans have been shown to have great sensitivity and specificity in the diagnosis of musculoskeletal infections, they are less commonly used. These images can also take some time to obtain, possibly requiring sedation. The use of a bone scan may be most helpful in cases where the site of infection is unclear. Tecnetium-99 m scanning is the most commonly used. Gallium or Indium tagged WBC can also be performed, though these may result in increased exam time, radiation exposure, and cost.

Laboratory

Laboratory workup is also incredibly valuable in the diagnosis of osteomyelitis as well as monitoring the treatment. Bloodwork typically obtained includes a CBC, ESR, CPR, and blood cultures. Cultures of the bone or deep abscesses can be obtained with ultrasound, fluoroscopic, or CT guidance, which can help guide antibiotic therapy.

As with most suspected infections, a complete blood count is typically obtained to evaluate for the elevated white count. In osteomyelitis, the presence of leukocytosis is variable [24]. This test also has poor reliability in monitoring treatment response. Though it may not be very helpful in the diagnosis or treatment of osteomyelitis, low WBC or platelets may point to a septic state or a neoplasm such as leukemia.

ESR and CRP are helpful inflammatory markers to evaluate for acute infection. ESR rises rapidly and is elevated in 90% of patients with osteomyelitis. CRP also rises rapidly and is elevated in approximately 98% of patients with acute osteomyelitis [24]. ESR can peak within 3–5 days; however, it may take weeks to normalize. This makes it less reliable in monitoring treatment response, whereas CRP declines rapidly in the setting of appropriate antibiotic therapy [25].

Blood or bone cultures can also be useful in diagnosis and treatment. Blood cultures are positive in less than half of the cases [26]. Cultures can be affected by antibiotics, so they should be obtained prior to beginning antibiotics. In an unstable patient, initiation of antibiotics should not be delayed in order to obtain cultures. Bone cultures can also be obtained, either intraoperatively or through image-guided

aspiration. In the surgical setting, it is also helpful to obtain biopsy tissue, in addition to cultures, as these may be needed to help rule out malignancy.

Management

Antibiotic Therapy

In cases of acute hematogenous or subacute osteomyelitis, antibiotic therapy alone may be sufficient to treat the infection. Infections that are diagnosed and treated early, those without significant intramedullary or subperiosteal abscesses, and those without other complicating factors may have success with antibiotics alone. Surgery may be avoided in those patients with an appropriate clinical response within a few days of treatment. The selection of antibiotic, route of administration, and duration of treatment are all somewhat controversial. A consultation with an infectious disease specialist can be very helpful in determining appropriate antibiotic coverage.

When the diagnosis of osteomyelitis is strongly suspected or confirmed, antibiotic therapy should begin as soon as possible. In children who appear well, with no signs of systemic illness, antibiotics may be held until cultures are obtained; though this delay should be minimal as the patient may rapidly deteriorate without treatment. Parenteral antibiotics are typically the initial treatment of choice. Empiric therapy can be altered based on local antimicrobial sensitivities and prevalence of certain organisms, factors which the Infectious Disease team will be aware of.

When beginning empiric therapy in children 3 months or younger, treatment is aimed at the most common causes of osteomyelitis including Staph aureus, gram-negative bacilli, and group B streptococcus. A third- or fourth-generation cephalosporin, as well as an anti-staphylococcal antibiotic, are preferred. Cephalosporins, such as ceftazidime or cefepime, are combined with vancomycin, clindamycin, or cefazolin to cover the organisms above. In children older than 3 months, the most common causes include Staph Aureus and other gram-positive organisms. Initial antibiotic therapy typically includes nafcillin/oxacillin, cefazolin, clindamycin, or vancomycin. Children with underlying conditions or risk factors may need additional empiric antibiotics, and consultation with an infectious disease specialist is often warranted. The initial antibiotics can be continued until cultures and sensitivities are available and organism-specific antibiotics can be initiated. In the large percentage of children with culture-negative osteomyelitis, empiric antibiotics may be continued so long as there is an appropriate clinical response to therapy.

Treatment can be monitored with the patient's clinical status, labs, and further imaging if necessary. With appropriate therapy, children typically exhibit clinical

improvement with decreased pain or swelling, improved range of motion or willingness to weight bear, as well as a decrease in fever if present. Persistent fevers, worsening pain, or pain in adjacent soft tissues or joints may indicate treatment failure. Serial laboratory workup should include CBC, ESR, and CRP. CRP is most useful in monitoring response to therapy and should gradually decline after initiating treatment. The CRP should usually decrease by 50% every 2–3 days [24]. Surgical intervention can also elevate the CRP, requiring a few more days to decrease. WBC count should also decline if elevated at the time of diagnosis. If the patient fails to improve based on the above, repeat imaging may be necessary to evaluate for worsening or spread of infection. Failure to respond to therapy may necessitate a change in antibiotics or surgical intervention.

Treatment with continued parenteral versus transition to oral antibiotics is controversial. Several studies suggest no difference in treatment success when comparing long-term parenteral antibiotics to those who transition to oral therapy [27, 28]. Switching to oral antibiotics is typically easier on the patient and their family as the use of home parenteral therapy necessitates the placement of a central venous catheter. In most cases, the switch from IV to oral antibiotics occurs after 5–10 days of therapy [28]. Children older than 1 month may be transitioned from IV to oral antibiotics if they respond well to the initial therapy and had no significant complications in their clinical course.

Treatment duration is typically a minimum of 4 weeks, although treatment may be extended in patients with a complicated clinical course, underlying medical conditions, or those who required surgical debridement. Clinical course can be monitored with outpatient office visits and weekly laboratory evaluations. Therapy should be continued until the patient has improved clinically and the ESR and CRP are normalized.

Surgery

Surgery may serve as an adjunct to antibiotic therapy in certain situations. Patients with concomitant deep soft tissue abscesses, intramedullary, or subperiosteal abscesses should undergo surgical debridement. Patients who fail to respond to antibiotic therapy, or those with chronic infections, may also benefit from surgical intervention.

The surgery itself entails the evacuation of abscesses, debridement of the surrounding tissues, irrigation of the surrounding tissues, and typically placement of a drain to help prevent reaccumulation of purulent fluid or formation of hematoma which can also serve as a nidus for infection. The surgeon may create a window in the bone to help decompress the intraosseous infection and provide further exposure for debridement (Fig. 28.5). Obtaining deep cultures is also an important benefit to surgery. Tissues can also be obtained for biopsy to rule out other diagnoses.

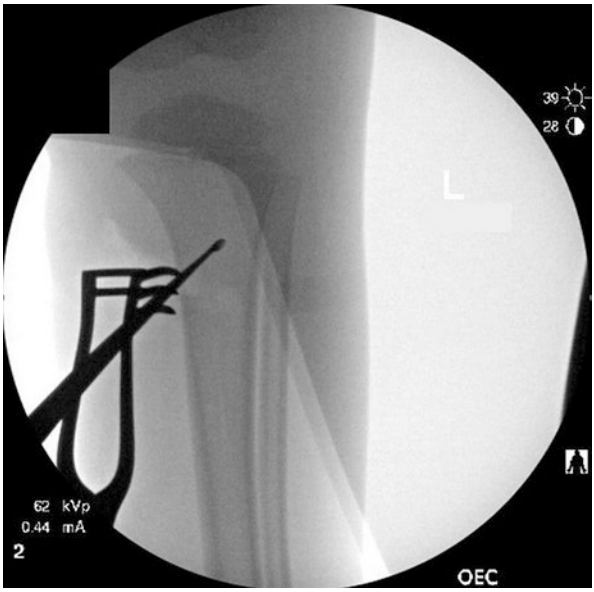


Fig. 28.5 Intraoperative fluoroscopy in a 2-year-old male with proximal tibial osteomyelitis. A curette is used to debride inside the bone through a cortical window

Natural History

Complications

There are many potential complications related to osteomyelitis. These may be avoided with early diagnosis and intervention. Complications related to destruction of the bone may include avascular necrosis, growth arrest or deformity, or even pathologic fractures. Other systemic complications include venous thrombosis or sepsis. Complications related to treatment including central line problems or medication side effects should also be monitored.

Since hematogenous osteomyelitis typically affects the metaphysis of long bones, the adjacent physis can be damaged by the inflammatory response. Damage to the physis may result in a physeal bar which can result in a disturbance of growth. A physeal bar located centrally can result in uniform shortening of the bone, but if this arrest occurs medially or laterally, it may result in an angular deformity as the child grows. The earlier this growth arrest occurs, the more significant the limb length discrepancy or angular deformity may become. Following children into adulthood may help in the early diagnosis of this complication [29].

Insult to the vascular supply of the bone can be caused by the body's inflammatory response to infection. This disruption may lead to necrosis of the bone termed avascular necrosis (AVN). AVN that occurs near the joint can lead to subchondral collapse and painful arthritic changes (Fig. 28.6). Large subperiosteal or intramedullary abscesses may also disrupt the blood flow to the bone, leading to necrosis and weakening of the bone in other locations. In this weakened state, a pathologic

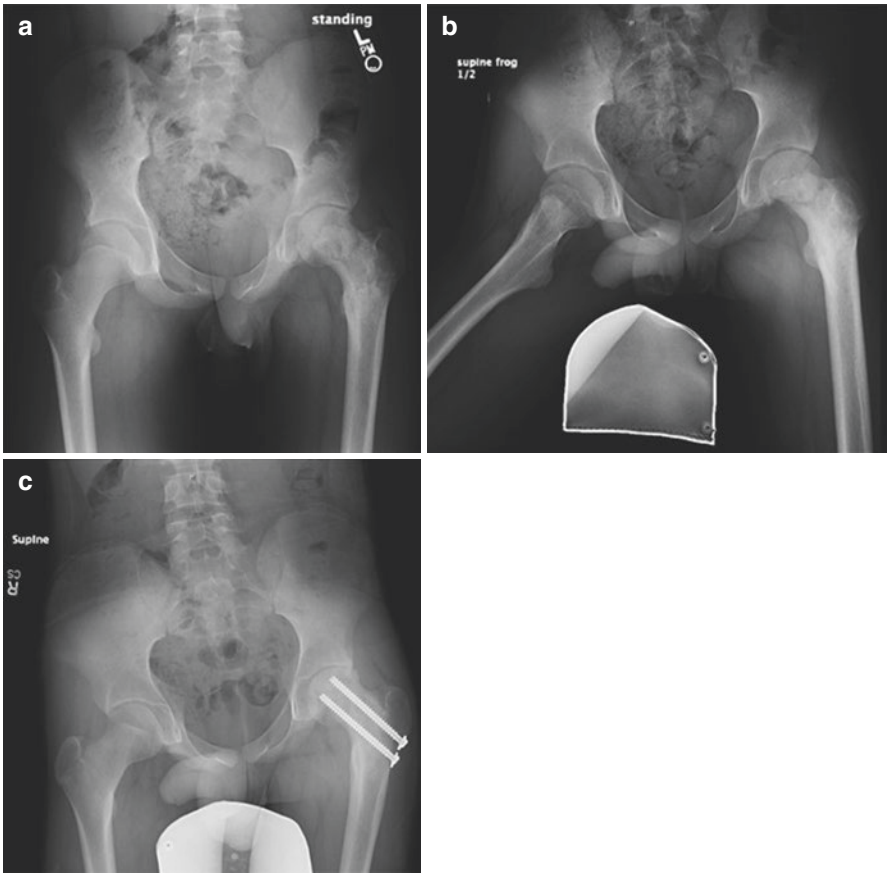


Fig. 28.6 (**a** and **b**) are AP and frog leg lateral radiographs of a 17-year-old male treated for left proximal femoral osteomyelitis and septic arthritis. Radiolucency concerning avascular necrosis is present in the femoral head and neck. The patient went on to develop left hip pain and prophylactic fixation was performed as demonstrated in Image (**c**)

fracture may occur. To limit this risk, it may be helpful to limit activity and protect weight bearing in patients with deep infections, also those treated surgically with a cortical window.

The infection can cause systemic changes which alter the coagulation pathways and increase the risk of deep vein thrombosis (DVT). Thrombus formation can occur in patients with certain risk factors. Patients infected with virulent strands of S. Aureus, commonly MRSA, have a higher risk of developing DVT [30]. Older children, those with markedly elevated CRP, or those requiring surgical intervention also have increased risk [31, 32]. Though this complication is infrequent, clinicians should have increased suspicion in children with these risk factors. Treatment typically includes therapeutic anticoagulation.

References

1. Sonnen GM, Henry NK. Pediatric bone and joint infections. Diagnosis and antimicrobial management. Pediatr Clin N Am. 1996;43(4):933–47.
2. Dartnell J, Ramachandran M, Katchburian M. Haematogenous acute and subacute paediatric osteomyelitis: a systematic review of the literature. J Bone Joint Surg Br. 2012;94(5):584–95.
3. Riise Ø, Kirkhus E, Handeland KS, Flatø B, Reiseter T, Cvancarova M, et al. Childhood osteomyelitis-incidence and differentiation from other acute onset musculoskeletal features in a population-based study. BMC Pediatr. 2008;45(8).
4. Gutierrez K. Bone and joint infections in children. Pediatr Clin N Am. 2005;52(3):779–94.
5. Wong M, Isaacs D, Howman-Giles R, Uren R. Clinical and diagnostic features of osteomyelitis occurring in the first three months of life. Pediatr Infect Dis J. 1995;14(12):1047–53.
6. Khachatourians AG, Patzakis MJ, Roidis N, Holtom PD. Laboratory monitoring in pediatric acute osteomyelitis and septic arthritis. Clin Orthop Relat Res. 2003;409:186–94.
7. Peltola H, Unkila-Kallio L, Kallio MJ. Simplified treatment of acute staphylococcal osteomyelitis of childhood. Pediatrics. 1997;99(6):846–50.
8. Everett ED, Hirschmann JV. Transient bacteremia and endocarditis prophylaxis. A review. Medicine (Baltimore). 1977;56(1):61–77.
9. Hobo T. Zur pathogenese de akuten haematogenen osteomyelitis, mit berucksichtigungder vitalfarbungs leher. Acta Scolar Med Kioto. 1921;4:1–29.
10. Speers DJ, Nade SM. Ultrastructural studies of adherence of Staphylococcus aureus in experimental acute hematogenous osteomyelitis. Infect Immun. 1985;49(2):443–6.
11. Trueta J. The normal vascular anatomy of the human femoral head during growth. J Bone Joint Surg Br. 1957;39(2):358–94.
12. Perlman MH, Patzakis MJ, Kumar PJ, Holtom P. The incidence of joint involvement with adjacent osteomyelitis in pediatric patients. J Pediatr Orthop. 2000;20(1):40–3.
13. Manche E, Rombouts-Godin V, Rombouts JJ. Acute hematogenous osteomyelitis due to ordinary germs in children with closed injuries. Study of a series of 44 cases. Acta Orthop Belg. 1991;57(2):91–6.
14. Labbé JL, Peres O, Leclair O, Goulon R, Scemama P, Jourdel F, et al. Acute osteomyelitis in children: the pathogenesis revisited? Orthop Traumatol Surg Res. 2010;96(3):268–75.
15. Morrissy RT, Haynes DW. Acute hematogenous osteomyelitis: a model with trauma as an etiology. J Pediatr Orthop. 1989;9(7):447–56.
16. Whalen JL, Fitzgerald RH Jr, Morrissy RT. A histological study of acute hematogenous osteomyelitis following physeal injuries in rabbits. J Bone Joint Surg Am. 1988;70(9):1383–92.
17. Tiku K, Tiku ML, Skosey JL. Interleukin 1 production by human polymorphonuclear neutrophils. J Immunol. 1986;136(10):3677–85.
18. Wong M, ID, Howman-Giles R, Uren R. Clinical and diagnostic features of osteomyelitis occurring in the first three months of life. Pediatr Infect Dis J. 1995;14(12):1047–53.
19. Nourse C, Starr M, Munckhof W. Community-acquired methicillin-resistant Staphylococcus aureus causes severe disseminated infection and deep venous thrombosis in children: literature review and recommendations for management. J Paediatr Child Health. 2007;43(10):656–61.
20. Bocchini CE, Hulten KG, Mason EO Jr, Gonzalez BE, Hammerman WA, Kaplan SL. Panton-Valentine leukocidin genes are associated with enhanced inflammatory response and local disease in acute hematogenous Staphylococcus aureus osteomyelitis in children. Pediatrics. 2006;117(2):433–40.
21. Ritz N, Curtis N. The role of Panton-Valentine leukocidin in Staphylococcus aureus musculoskeletal infections in children. Pediatr Infect Dis J. 2012;31(5):514–8.
22. Yagupsky P, Erlich Y, Ariela S, Trefler R, Porat N. Outbreak of Kingella kingae skeletal system infections in children in daycare. Pediatr Infect Dis J. 2006;25(6):526–32.
23. Capitanio MA, Kirkpatrick JA. Early roentgen observations in acute osteomyelitis. Am J Roentgenol Radium Therapy, Nucl Med. 1970;108(3):488–96.

24. Unkila-Kallio L, Kallio MJ, Eskola J, Peltola H. Serum C-reactive protein, erythrocyte sedimentation rate, and white blood cell count in acute hematogenous osteomyelitis of children. Pediatrics. 1994;63(1):59–62.
25. Pääkkönen M, Kallio MJ, Kallio PE, Peltola H. Sensitivity of erythrocyte sedimentation rate and C-reactive protein in childhood bone and joint infections. Clin Orthop Relat Res. 2010;468(3):861–6.
26. Zhorne DJ, Altobelli ME, Cruz AT. Impact of antibiotic pretreatment on bone biopsy yield for children with acute hematogenous osteomyelitis. Hosp Pediatr. 2015;5(6):337–41.
27. Nelson JD, Bucholz RW, Kusmiesz H, Shelton S. Benefits and risks of sequential parenteral—oral cephalosporin therapy for suppurative bone and joint infections. J Pediatr Orthop. 1982;2(3):255–62.
28. Zaoutis T, Localio AR, Leckerman K, Saddlemire S, Bertoch D, Keren R. Prolonged intravenous therapy versus early transition to oral antimicrobial therapy for acute osteomyelitis in children. Pediatrics. 2009;123(2):636–42.
29. Peters W, Irving J, Letts M. Long-term effects of neonatal bone and joint infection on adjacent growth plates. J Pediatr Orthop. 1992;12(6):806–10.
30. Martin E, Cevik C, Nugent K. The role of hypervirulent Staphylococcus aureus infections in the development of deep vein thrombosis. Thromb Res. 2012;130(3):302–8.
31. Amaro E, Marvi TK, Posey SL, Benvenuti MA, An TJ, Dale KM, et al. C-reactive protein predicts risk of venous thromboembolism in pediatric musculoskeletal infection. J Pediatr Orthop. 2019;39(1):e62–7.
32. Hollmig ST, Copley LA, Browne RH, Grande LM, Wilson PL. Deep venous thrombosis associated with osteomyelitis in children. J Bone Joint Surg Am. 2007;89(7):1517–23.

Chapter 29
Orthopedic Manifestations of In Utero Exposures to Teratogens/Infections

Jill E. Larson

Epidemiology and Pathology

While birth defects are common (2–3% of all newborns), it is far more common to have a genetic etiology than a teratogen or infectious etiology for the congenital birth abnormality. In fact, The Food and Drug Administration (FDA) (2005b) estimates that less than 1% of all birth defects are caused by a teratogen or medication [1]. The definition of a teratogen may be a drug or other chemical substance, a physical or environmental factor such as heat or radiation, a maternal metabolite such as in phenylketonuria or diabetes, a genetic abnormality, or an infection.

During the first 2 weeks of gestation, teratogenic agents usually kill the embryo rather than cause congenital malformations. Major malformations are more common in early embryos than in newborns; however, most severely affected embryos are spontaneously aborted during the first 6–8 weeks of gestation. During organogenesis between days 15 and 60, teratogenic agents are more likely to cause major congenital malformations and the eventual orthopedic manifestations that are diagnosed and treated postnatally [1].

See Table 29.1 for a list of the most common teratogens that will be outlined in this chapter.

Nicotine

Nicotine does not produce congenital malformations, but nicotine does have an effect on fetal growth. Maternal smoking is a well-established cause of intrauterine growth restriction. Heavy cigarette smokers were also more likely to have a

J. E. Larson (✉)
Ann & Robert H. Lurie Children's Hospital, Chicago, IL, USA
e-mail: jlarson@luriechildrens.org

J. F. Sarwark, R. L. Carl (eds.), *Orthopaedics for the Newborn and Young Child*,
https://doi.org/10.1007/978-3-031-11136-5_29

Table 29.1 List of the most common teratogens and type of teratogen

Teratogen	Type
Nicotine	Chemical
Ethanol/alcohol	Chemical
Tetracycline	Chemical
Phenytoin (anticonvulsants)	Chemical
Chemotherapeutic agents	Chemical
Retinoic acid	Chemical
Thalidomide	Chemical
Radiation	Ionizing
Hyperglycemia (maternal diabetes)	Unknown
Amniotic band	Mechanical
Hyperthermia	Inductive
Arsenic	Chemical

premature delivery, which is a risk factor for cerebral palsy. The orthopedic manifestations of cerebral palsy include increased muscular tone, joint contractures, hip instability, spinal deformity, and foot deformities (see Chap. 52 on Cerebral Palsy for more details).

Ethanol

Alcohol is a common drug abused by women of childbearing age. Infants born to alcoholic mothers demonstrate prenatal and postnatal growth deficiency, mental retardation, and other malformations. Fetal alcohol syndrome occurs at a frequency of 1 in 300 lives births in the United States. The classical facial features associated with fetal alcohol syndrome include short palpebral fissures, maxillary hypoplasia, and a smooth philtrum. The specific orthopedic manifestations of fetal alcohol syndrome include limb defects such as camptodactyly (short distal phalanges), syndactyly, and small fifth fingernails [2, 3].

Tetracycline

Tetracycline, the type of antibiotic, can cross the placental membrane and is deposited in the embryo in bones and teeth. Tetracycline exposure can result in yellow staining of the primary or deciduous teeth and diminished growth of the long bones. Tetracycline exposure after birth has similar effects.

Anticonvulsants (Phenytoin)

Anticonvulsant agents such as phenytoin produce the fetal hydantoin syndrome consisting of intrauterine growth retardation, microcephaly, mental retardation, distal phalangeal hypoplasia, and specific facial features. Further orthopedic manifestations include shortness of the metacarpals, cone-shaped epiphyses, limited movements at interphalangeal joints, and tapering fingers with nail hypoplasia. These congenital malformations occur in approximately one-third of children whose mothers are taking this drug during pregnancy [2].

Valproic acid is associated with a 20-fold increase incidence of spina bifida in children born to pregnant mothers undergoing valproic acid treatment. Valproic acid has also been associated with axial skeletal dysmorphogenesis such as block vertebrae and hemivertebrae [4] (see Fig. 29.1). Folic acid administration can significantly reduce the incidence of experimentally induced valproic acid axial skeletal defects [5].

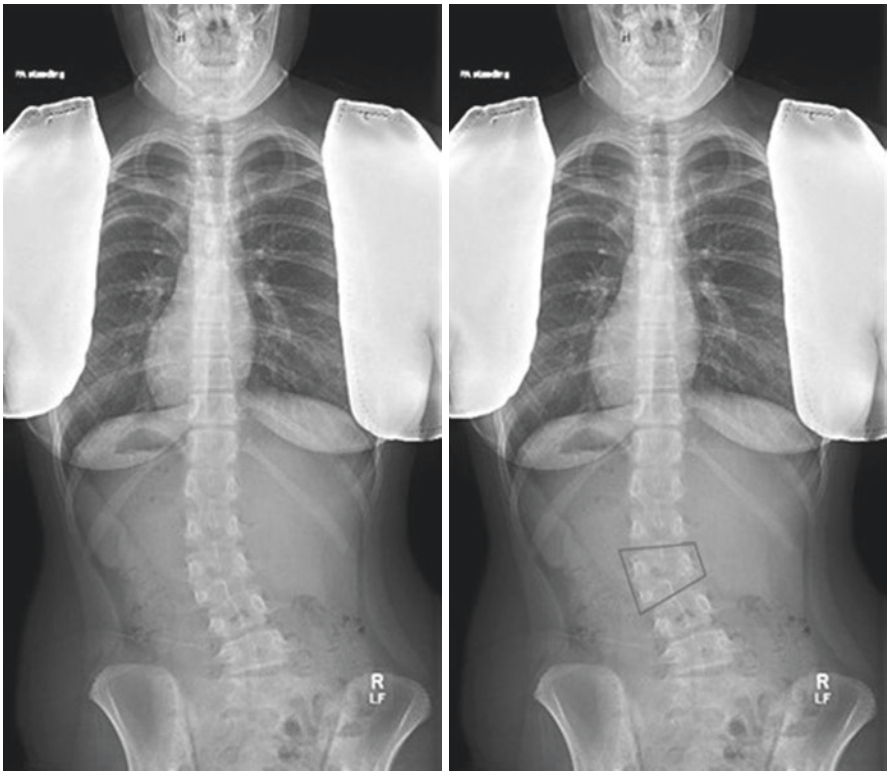


Fig. 29.1 Standing PA radiograph of the entire spine demonstrating a hemivertebrae between L3 and L4 and associated scoliosis. Partial fusion of the hemivertebra to the L3 level creates the trapezoidal structure highlighted

Chemotherapeutic Agents

Anti-neoplastic or chemotherapeutic agents are highly teratogenic as these agents inhibit rapidly dividing cells. These medications should be avoided whenever possible but are occasionally used in the third trimester when they are urgently needed to treat the mother [1].

Retinoic Acid

Retinoic acid or vitamin A derivatives are extremely teratogenic in humans. Even at very low doses, oral medications, such as isotretinoin, used in the treatment of acne, are potent teratogens. The critical period of exposure appears to be from the second to the fifth week of gestation. A commonly used form of retinoic acid is isotretinoin (Accutane), which was discovered to cause notable structural defects in infants in 1985. The most common malformations include craniofacial dysmorphisms, cleft palate, thymic aplasia, and neural tube defects. There have been no affected babies born to women who stopped taking isotretinoin before the 15th day following conception [6].

Thalidomide

The tranquilizer thalidomide is one of the most famous and notorious teratogens. This hypnotic agent was used widely in Europe in 1959, after which an estimated 7000 infants were born with thalidomide syndrome or meromelia. It has since been banned and withdrawn in 1962, but the characteristic features of this syndrome include limb abnormalities that span from absence of the limbs to rudimentary limbs to abnormally shortened limbs. Additionally, thalidomide also causes malformations of other organs including absence of the internal and external ears, hemangiomas, congenital heart disease, and congenital urinary tract malformations. The critical period of exposure appears to be 24–36 days after fertilization [2].

Ionizing Radiation

Ionizing radiation can injure the developing embryo due to cell death or chromosome injury. The severity of damage to the embryo depends on the dose absorbed and the stage of development at which the exposure occurs. A study of survivors of the Japanese atomic bombing demonstrated that exposure at 10–18 weeks of pregnancy is a period of greatest sensitivity for the developing brain [1].

There is no proof that human congenital malformations or postnatal orthopedic manifestations have been caused by diagnostic levels of radiation. However, attempts are made to minimize scattered radiation from diagnostic procedures such

as x-rays that are not near the uterus. The standard dose of radiation associated with a diagnostic x-ray produces a minuscule risk to the fetus. However, all women of childbearing age are asked if they are pregnant before any exposure to radiation.

Mechanical Forces

Mechanical forces can also act as teratogens. Malformations of the uterus may restrict fetal movements and be associated with congenital dislocation of the hip and clubfoot. Oligohydramnios can have similar results and mechanically induce abnormalities of the fetal limbs. These abnormalities would be classified as deformations or abnormal forms, shapes, or positions of body parts caused by physical constraints. Amniotic bands are fibrous rings and cause intrauterine amputations or malformations of the limbs as well (see Fig. 29.2). These abnormalities would be classified as disruptions or defects from interference with a normally developing organ system usually occurring later in gestation.

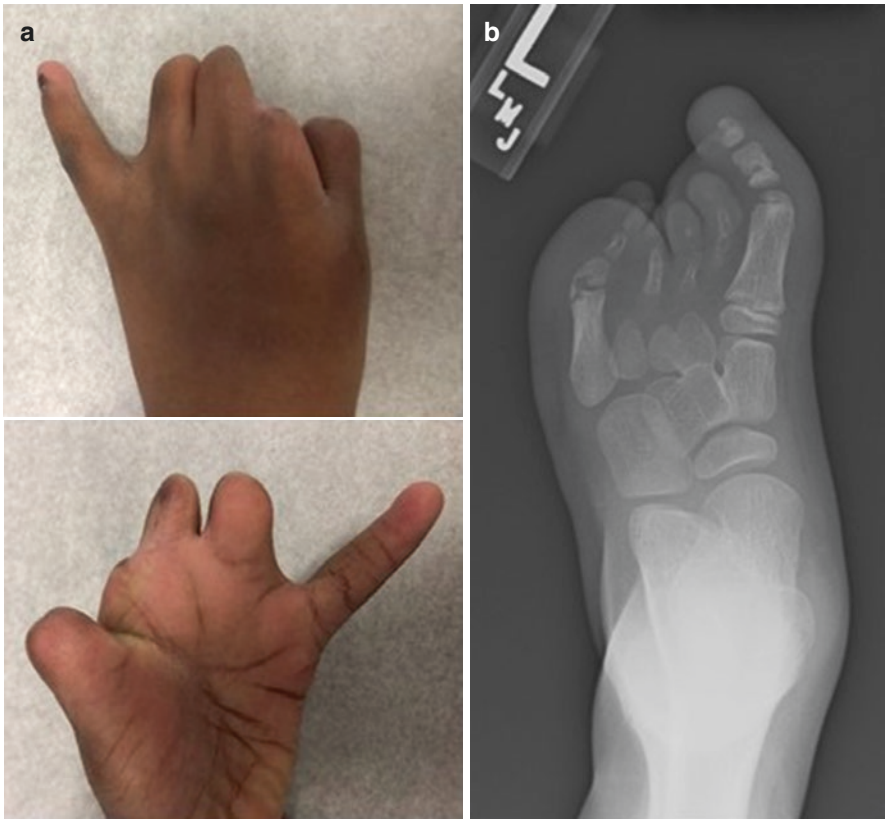


Fig. 29.2 (**a**) clinical photos of a hand with digital amputations secondary to amniotic bands. (**b**) radiographic image of foot with malformations due to amniotic bands

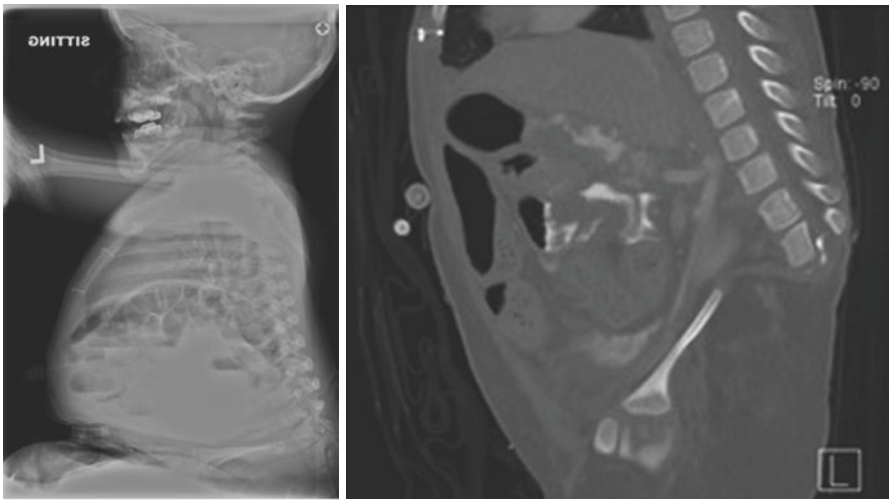


Fig. 29.3 A sitting lateral radiographic and supine sagittal cut of a CT scan demonstrating complete agenesis of the sacrum with discontinuity between the spinal column and pelvis

Hyperglycemia: Maternal Diabetes

Children born to diabetic mothers have a two- to eightfold increased risk of congenital anomalies than the general population. Orthopedic malformations include neural tube defects, preaxial hallucal polydactyly, femoral hypoplasia, and decreased muscle tone. The most extreme form of a neural tube defect is caudal regression syndrome or sacral agenesis (see Fig. 29.3) This axial defect occurs 200 times more frequently in diabetic pregnancies than in normal pregnancies [2, 4].

Hyperthermia

Exposure of a fetus to high temperatures (> 2 °C above normal) is associated with neural tube defects, such as spina bifida [4].

Arsenic

Arsenic is a metal pollutant found naturally in groundwater and in mine waste, agricultural runoff, and industrial by-products. It is toxic to humans and is known to cause birth defects, most notably spina bifida within the orthopedic community. It is also known to cause craniofacial defects [4].

Nitrosable Drugs

Exposure to nitrosable drugs such as amoxicillin, caffeine, chlorpheniramine, promethazine, and pseudoephedrine in the first trimester, has been shown to be associated with fetal neural tube defects (such as spina bifida) as well as both transverse and longitudinal limb deficiencies [7]. However, studies have also demonstrated that prevention/treatment for nitrosable drug exposure can be achieved with an estimated maternal daily dietary vitamin C intake above 85 mg, which significantly lowers the odds ratio for limb deficiencies [8].

Infections: TORCH

The pneumonic "TORCH" (see Table 29.2) can help practitioners remember the most common perinatal infections that can cause fetal malformations. In general, perinatal infections account for 2–3% of all congenital anomalies [9].

Toxoplasmosis

The prevalence of toxoplasmosis infections is approximately 1 in 10,000 live births in the United States. There are no specific orthopedic manifestations from prenatal exposure to toxoplasmosis, but children can suffer from epilepsy, intellectual disability, and visual disabilities (such as chorioretinitis, cataracts, and glaucoma into adulthood).

Table 29.2 Perinatal infections that can cause fetal malformations and congenital anomalies

	"TORCH" infections in the perinatal period
T	Toxoplasmosis
O	Other: syphilis and varicella
R	Rubella (congenital)
C	Cytomegalovirus
H	Herpes

Other: Syphilis and Varicella

Symptoms of congenital syphilis differ between newborns and older infants because the disease progresses from its secondary stage to its final phase. Newborns suffer from failure to thrive, irritability, watery nasal discharge, rash, and lesions (early rash of small blister on palms and soles or feet with a later rash of copper-colored lesions on palms, soles, and face) and severe pneumonia. This is in contrast to older infants who suffer from tooth abnormalities (notched and peg-shaped teeth), bone pain, pseudo paralysis, blindness, and deafness. Joint swelling is the most common orthopedic manifestation of the infection in a newborn although dactylitis with hand swelling, pathologic fracture secondary to bone infections and soft tissue swelling are other presenting symptoms. With appropriate treatment for syphilis, the osseous abnormalities will demonstrate complete healing and normal growth following treatment [10].

There have been case reports of fetal varicella syndrome related to woman who had chicken pox during early gestation. The most commonly reported orthopedic manifestations include hypoplasia of the libs with or without rudimentary digits, atrophy of limbs, and clubfoot. Other orthopedic manifestations that have been described include underdeveloped clavicle, scapula, and rib; scoliosis [11].

Congenital Rubella

Congenital rubella or German measles consists of the triad of cataracts, cardiac malformation, and deafness. The earlier in the pregnancy that the embryo is exposed to maternal rubella, the greater the likelihood that it will be affected. Most infants exposed during the first 4–5 weeks after fertilization will have stigmata of this exposure if the fetus survives until term. Exposure to rubella during the second and third trimester results in a much lower frequency of malformation but continues to pose a risk of mental retardation and hearing loss. Radiographic evidence of congenital rubella is notable for linear areas of increased bone density parallel to the longitudinal axis combined with areas of radiolucency leading to the “celery stick” appearance. While spontaneous pathological fractures have been reported, recovery is usually complete and rapid without long-term sequelae, and thus orthopedic manifestations are not typically associated with congenital rubella [12].

Cytomegalovirus

Congenital cytomegalovirus infection is the most common viral infection of the fetus. Infection of the early embryo during the first trimester most commonly results

in spontaneous termination. Exposure later in the pregnancy results in intrauterine growth retardation, micromelia, chorioretinitis, blindness, microcephaly, cerebral calcifications, mental retardation, and hepatosplenomegaly. Currently, CMV is the most common cause of congenital infection in the United States. 10–20% of infected infants may suffer sensorineural hearing loss, ocular damage, or impairment of cognitive and motor function. The orthopedic manifestations of CMV include limb atrophy, limb deficiencies, malformations, and underdevelopment. The neurologic sequelae of CMV can also cause cerebral palsy and the resultant orthopedic consequences related to increased muscle tone and joint contractures. CMV is common in all socioeconomic groups but the subpopulation with the highest rates of congenital disease is young, single, nonwhite mothers [13].

Herpes

Congenital herpes simplex Virus (HSV) infections are rare, but can present with microcephaly, hydrocephalus, and chorioretinitis at birth. Postnatal acquisition of HSV is almost always due to HSV-1 and is associated with contact with hospital personnel or family members who are shedding HSV-1, which usually results from exposure to HSV during delivery. Orthopedic manifestations of HSV are rare or nonexistent unless there is central nervous system (CNS) involvement. A CNS-associated infection, which comprises 30% of most large case series, is associated with lethargy, poor feeding, or seizures, with or without cutaneous lesions. Morbidity of CNS HSV in infants is higher with HSV-2 than HSV-1 and may include developmental delay, epilepsy, blindness, and cognitive disabilities. CNS involvement can lead to a cerebral palsy-type picture with increased muscle tone, contractures, neuromuscular hip dysplasia, or scoliosis, which may need to be addressed by tone management, bracing, or surgical intervention [14].

References

1. Cunningham FG, Leveno KJ, Bloom SL, Spong CY, Dashe JS, Hoffman BL, et al. Chapter 12: Teratology, teratogens, and fetotoxic agents. In: Williams obstetrics. McGraw-Hill Education; 2014.
2. Alexander PG, Clark KL, Tuan RS. Prenatal exposure to environmental factors and congenital limb defects. Birth Defects Res C Embryo Today. 2016;108(3):243–73. https://doi.org/10.1002/bdrc.21140. Epub 2016 Oct 21.
3. Jones KL, Jones MC, del Campo M. Fetal alcohol syndrome chapter in Smith's Recognizable Patterns of Human Malformations. Philadelphia, PA: Elsevier Saunders; 2013.
4. Alexander PG, Tuan RS. Role of environmental factors in axial skeletal dysmorphogenesis. Birth Defects Res C Embryo Today. 2010;90(2):118–32. https://doi.org/10.1002/bdrc.20179.
5. Greene ND, Copp AJ. Mouse models of neural tube defects: investigating preventive mechanisms. Am J Med Genet C Semin Med Genet. 2005;135C(1):31–41.

6. Jones KL, Jones MC, del Campo M. Retinoic acid embryopathy (accutane embryopathy) in Smith's recognizable patterns of human malformations. Philadelphia, PA: Elsevier Saunders; 2013.
7. Brender JD, Werler MM, Shinde MU, Vuong AM, Kelley KE, Huber JC Jr, et al. Nitrosatable drug exposure during the first trimester of pregnancy and selected congenital malformations. Birth Defects Res A Clin Mol Teratol. 2012;94(9):701–13. https://doi.org/10.1002/bdra.23060. Epub 2012 Aug 18.
8. Shinde MU, Vuong AM, Brender JD, Werler MM, Kelley KE, Huber JC Jr, et al. Prenatal exposure to nitrosatable drugs, vitamin C, and risk of selected birth defects. Birth Defects Res A Clin Mol Teratol. 2013;97(8):515–31. https://doi.org/10.1002/bdra.23137. Epub 2013 May 28.
9. Stegmann BJ, Carey JC. TORCH infections. toxoplasmosis, other (syphilis, varicella-zoster, parvovirus B19), rubella, cytomegalovirus (CMV), and herpes infections. Curr Womens Health Rep. 2002;2(4):253–8.
10. Rasool MN, Govender S. The skeletal manifestations of congenital syphilis. A review of 197 cases. J Bone Joint Surg Br. 1989;71(5):752–5.
11. Jones KL, Jones MC, del Campo M. Fetal varicella syndrome in Smith's recognizable patterns of human malformations. Philadelphia, PA: Elsevier Saunders; 2013.
12. Denante S, Brevaut-Malaty V, Coze S. Panuel M Newborn with transient macular rash and thrombocytopenia. Skeletal manifestations of congenital rubella syndrome. Skelet Radiol. 2017;46(11):1559, 1603–4. https://doi.org/10.1007/s00256-017-2693-7.
13. Swanson EC, Schleiss MR. Congenital cytomegalovirus infection: new prospects for prevention and therapy. Pediatr Clin N Am. 2013;60(2):335–49. https://doi.org/10.1016/j.pcl.2012.12.008.
14. Corey L, Wald A. Maternal and neonatal herpes simplex virus infections. N Engl J Med. 2009;361(14):1376–85.

Chapter 30
Leukemia in the Newborn and Young Child

Parker D. Plant and Merritt E. Adams

Overview and Epidemiology

Cancer in children is a rare disease. The annual incidence rate of cancer in children and adolescents in the United States is 186.6 per one million children aged birth to 19 years with an annual rate increase of 0.6% since 1975 [1]. The primary childhood cancer is hematologic malignancy, which composes 40% of childhood cancers. This contrasts with adults, in whom solid tumor malignancies predominate [2]. Leukemia is the most common childhood cancer, comprising approximately 30–40% of all childhood cancers and has been historically classified into four subtypes based on clinical presentation and morphological appearance of the malignant cells [2]. Acute Lymphoblastic Leukemia (ALL) is the most common subtype and accounts for 80% of all childhood leukemias. Acute Myelogenous Leukemia (AML) accounts for 15–20% and Chronic Myelogenous Leukemia (CML) accounts for 2–5%. Chronic Lymphoblastic Leukemia (CLL) is a form rarely seen in childhood or adolescence [1–3]. The incidence of leukemia is greater in males than females. Additionally, Caucasian and Hispanic children have a much higher incidence than African American children. There is also a greater risk of ALL in more developed countries or with higher socioeconomic status. There is no clear explanation for this finding [1, 2].

P. D. Plant
Department of Pediatrics, Erlanger Hospital, Chattanooga, TN, USA

M. E. Adams (✉)
Department of Orthopedic Surgery, Children's Hospital at Erlanger, UT College of Medicine Chattanooga, Chattanooga, TN, USA
e-mail: merritt.adams@erlanger.org

J. F. Sarwark, R. L. Carl (eds.), *Orthopaedics for the Newborn and Young Child*,
https://doi.org/10.1007/978-3-031-11136-5_30

Pathophysiology

Leukemia results from expansion of malignant hematopoietic or lymphoid cells. This expansion primarily occurs in the bone marrow and the leukemic cellular proliferation is usually monoclonal [2, 4]. While the cause remains unknown in most children, both environmental and genetic factors may contribute to the development of leukemia. There is documented association of leukemia with inherited predisposing genetic syndromes, such as Trisomy 21, Bloom's Syndrome, ataxia-telangiectasia, Klinefelter syndrome, Fanconi anemia, and Nijmegen breakage syndrome [5]. Also, certain environmental and chemical factors such as ionizing radiation exposure and benzene exposure have an established role in leukemogenesis [2]. Due to the increasing incidence of childhood leukemia, two theories centered on population-mixing and delayed-infection hypotheses have emerged to explain the association of genetics and environmental factors in the pathogenesis of childhood leukemia [5].

Common Clinical Presentation

The clinical presentation of leukemia results from both the direct and indirect effects of malignant cell proliferation within the bone marrow and other organs [2]. Leukemic blasts most commonly involve the extramedullary organs of the liver, spleen, and lymph nodes with resultant organomegaly, but leukemia also has the potential to involve any body organ, including skin, kidney, lung, pleura, pericardium, eye, breast, ovaries, and GI tract [2].

Many of the initial signs and symptoms of leukemia are due to the disruption of normal hematopoiesis. Anemia may result in pallor, fatigue, and decreased appetite. Neutropenia may be associated with fever and an increased risk of severe infection, which is the major life-threatening complication for a child with acute leukemia. Thrombocytopenia and coagulation factor deficiencies may cause increased bleeding, petechiae, and ecchymoses. Additionally, due to the leukemic blasts present in bone marrow, bone pain is reported as a common finding [2, 6]. Other signs and symptoms may include renal involvement due to leukemia infiltration that results in elevated uric acid concentrations and other electrolyte abnormalities.

Evaluation and Diagnosis

The diagnosis of childhood leukemia generally focuses on direct observation for leukemic blasts within both the peripheral blood and bone marrow and additional testing for leukemia differentiation. Bone marrow studies are essential for a

conclusive diagnosis of leukemia because malignant leukemia blast cells are not always observed circulating in the blood and other conditions such as infectious mononucleosis occasionally can result in large numbers of atypical white cells in the blood. The exact peripheral blood minimum blast percentage has also not been defined for an accurate diagnosis in pediatrics, whereas a marrow blast percentage >20% is confirmatory for leukemia [2, 7].

For a greater focus on orthopedic manifestations of childhood leukemia, most of the discussion in this chapter will focus on the diagnosis of Acute Lymphoblastic Leukemia (ALL) and its variants. ALL is distinguished by its morphologies, immunotyping, and cytogenetics. Immunophenotyping of leukemic lymphoblasts by flow cytometry establishes the correct diagnosis and defines cell lineage. Despite the various subclassifications of ALL, the only findings of major therapeutic importance are T cell, mature B cell, and B cell precursor phenotypes [5]. Another factor to consider in the diagnosis of ALL is determining high-risk vs low-risk in terms of treatment options and prognosis. Generally, ALL is determined to be of high risk if it consists of a T cell lineage, has CNS involvement, testicular involvement in males, WBC >50,000, age <1 or >10, or certain genetic factors that confer a worse prognosis, i.e., Philadelphia chromosome or diploidy.

Treatment and Management

The mainstay of leukemia treatment is chemotherapy and bone marrow transplant as necessary. The goal of chemotherapy is to induce clinical and biological remission by eliminating the malignant cell line. The type of leukemia and clinical response dictates the various protocol and cycles of leukemia that a patient receives. Patients can also enroll in several therapeutic studies at Pediatric Oncology Centers, which may alter the treatment plan [2]. Generally, ALL will require an induction phase to induce remission, followed by consolidation therapy to focus on CNS involvement. Delayed intensification, which consists of reinduction and/or reconsolidation may follow depending on the protocol. Maintenance therapy is then given to ensure remission and complete recovery. In patients with AML, induction therapy is generally followed by bone marrow transplant if a proper match is found. If no proper match exists, induction can be intensified [8].

With the advent of chemotherapy and other treatments over the past several decades, the survival of patients with leukemia has improved dramatically. Before chemotherapy, the median survival for a newly diagnosed acute leukemia patient was 3 months [2]. Currently, the 5-year overall survival rate for ALL patients is 92% [9]. The overall survival rate of AML patients is now 60–70% with event-free survival exceeding 50% [10].

Current research focuses on continued understanding of the biology of leukemia with biomarkers for better risk stratification and testing novel agents and treatment

strategies for those predicted to have a poor outcome. Additional emphasis is also being placed on enhancing supportive care to decrease morbidity and mortality and improve short- and long-term quality of life [9, 10].

Orthopedic Manifestations

A discussion of the orthopedic manifestations seen in pediatric leukemia patients must first focus on the importance of the ability of both primary care providers and orthopedic specialists to recognize early and late primary orthopedic manifestations of leukemia. Furthermore, it is equally important for these same providers to recognize the secondary or indirect orthopedic manifestations that can accompany the treatment of leukemia. Other important items include the proper diagnostic measures, imaging modalities, and treatments that accompany each orthopedic manifestation.

Acute leukemia, and more specifically, Acute Lymphoblastic Leukemia (ALL) can mimic several orthopedic pathologies at presentation. In some patients, musculoskeletal complaints are the only apparent abnormality with the absence of medullary signs and symptoms. The history and clinical examination can be misleading and hematological and radiological investigations are not pathognomonic. This may cause a delay in the diagnosis of leukemia, resulting in higher morbidity and mortality due to the progression of symptoms and lack of proper treatment [6, 11, 12]. Due to this possibility of delay in diagnosis and treatment, orthopedic and pediatric health care providers should be aware of the common musculoskeletal findings, either clinically or radiologically in leukemia, and should suspect leukemia in any child with unexplained persistent skeletal pain or radiographic alterations [3].

Generally, 25% of children with acute leukemia, with the majority being ALL, have some type of musculoskeletal manifestation with one study reporting rates as high as 59% [3]. Bone radiographic abnormalities are reported in 40–75% of patients at presentation and rise to 70–90% during the course of disease and treatment [3, 12]. The most common clinical symptoms include bone pain, functional impairment, limping, swelling, and joint effusion. Radiographic findings include osteolysis, metaphyseal bands, osteopenia, osteosclerosis, pathological fractures, periosteal reactions, and mixed lysis-sclerosis lesions, with avascular necrosis, vertebral collapses, and osteolysis appearing as late findings [3, 12].

Primary Musculoskeletal Signs and Symptoms

Primary musculoskeletal signs and symptoms refer to those caused by the direct effects of leukemia via bone or joint involvement or the musculoskeletal system in general [6, 13]. The most common primary musculoskeletal complaints are listed in Table 30.1.

Table 30.1 Primary leukemic musculoskeletal symptoms [3, 6, 12, 13]

Symptom	Incidence
Bone pain	15–30%
Limping	5–15%
Swelling	10%
Joint effusion	6%

Bone Pain

Bone pain is related to the large-scale production and expansion of hematopoietic cells in the bone marrow cavities of both long bones and vertebrae or direct infiltration of the periosteum and bone by leukemic cells [6, 12].

Limping

Limping is due to the generalized bone pain that occurs primarily in the long bones and additional joint involvement, limping represents a functional impairment that commonly presents in children with acute leukemia.

Joint Pain

Joint pain is usually referred to pain from periosteal lesions in the adjacent metaphysis rather than direct infiltration of leukemia cells into the synovia. This type of pain is often migratory, and in some cases, when combined with swelling and synovial effusion may appear to represent manifestations of other conditions such as juvenile idiopathic arthritis, rheumatic fever, or septic arthritis (Fig. 30.1) [14].

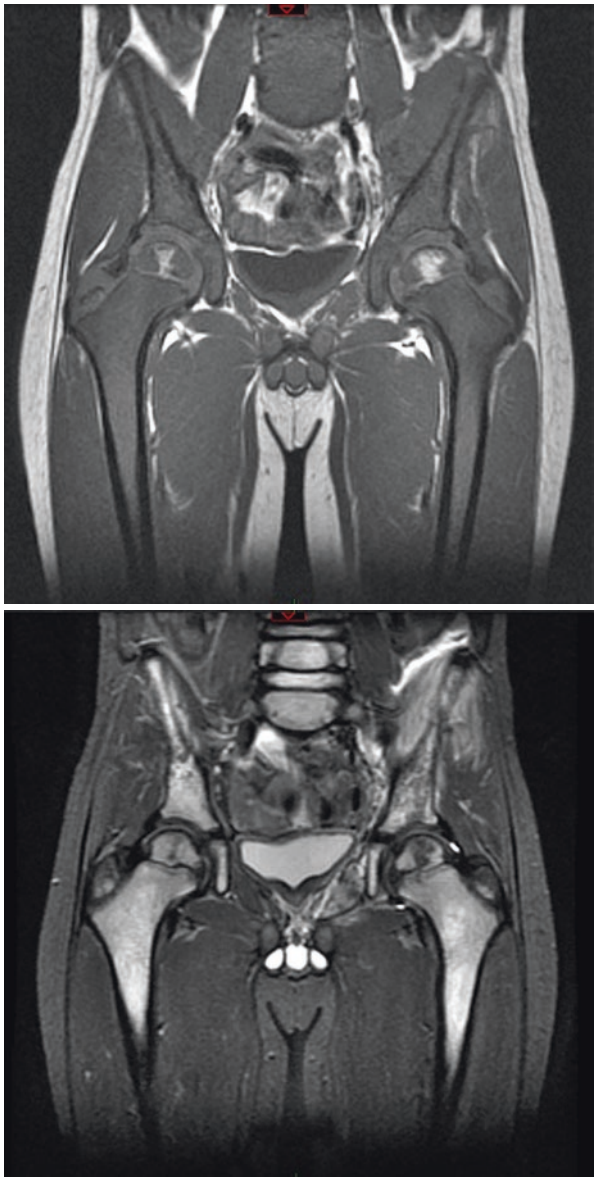


Fig. 30.1 MRI findings in a 4-year-old male who presented with bilateral hip pain and limping with the left side greater than the right side. Initial concern for septic arthritis. Diagnosed as osteonecrosis due to acute leukemia

Secondary Musculoskeletal Signs and Symptoms

Secondary signs and symptoms generally refer to those musculoskeletal signs and symptoms that occur due to indirect effects of leukemia or side effects of treatment, mainly with chemotherapy. These include avascular necrosis, reduced bone mineral density, osteoporosis, and growth impairment [6]. There are also several documented cases of pyomyositis associated with induction chemotherapy and the resulting immunocompromised state [15, 16].

Radiologic Manifestations and Abnormalities

Acute leukemia is associated with several radiographic osseous abnormalities (Table 30.2) including, osteoporosis, metaphyseal bands (leukemic lines), osteopenia, and less frequently, sclerotic lesions, and periosteal new bone formation. These radiological changes, while not pathognomonic, can be highly suggestive of leukemia. Additionally, avascular necrosis is commonly associated with leukemia, but this occurs primarily as a side effect of corticosteroid treatment in leukemia. Typically, a bone scan is most helpful in distinguishing leukemic musculoskeletal manifestations from other orthopedic conditions or tumors. Other modalities such as MRI are helpful in accurately defining the location and size of intra- and extraosseous involvement [6].

Table 30.2 Radiologic manifestations and abnormalities of leukemia [3, 6, 12]

Finding	Incidence
Osteoporosis	40–60%
Pathologic fractures	20%
Osteolytic lesions	10–50%
Metaphyseal bands	5–10%
Periosteal reactions	4–7%
Osteosclerosis	3–7%

Osteoporosis

Osteoporosis is related to changes in bone metabolism with the reduction in bone trabecula levels and thinning of the cortex. There is diffuse infiltration of leukemic cells in bone and bone marrow, most commonly located in the spine. Degree and severity increase after the introduction of steroids and chemotherapy. Demineralization process is gradual but tends to slow down during pathological remission [6, 12].

Metaphyseal Bands

Metaphyseal bands are the results of generalized metabolic dysfunction that disrupts the osteogenesis at the epiphyseal growth plate. They range from 2 to 15 mm in length and histologically appear as bone trabecula reduces in both number and dimension [6, 12].

Lytic Bone Lesions

Lytic bone lesions are a combination of leukemic infiltration of the bone marrow, local hemorrhage, and osteonecrosis of adjacent bone. They typically involve flat and tubular bones, such as the metaphysis of long bones [6, 12].

Osteosclerosis

Osteosclerosis develops due to abnormal reactive new bone formation secondary to infiltration of leukemic cells, commonly affecting metaphysis of long bones [6, 12].

Periosteal Reactions

Periosteal reactions are due to the buildup of leukemic cells that detach periosteum from the bone cortex. They may also be caused by leukemic bleeding diathesis [12].

Pathologic Fractures

Pathologic fractures are due to widespread osteoporosis and lytic lesions, which can predispose to fractures. Vertebral fractures should cause any orthopedist to consider acute leukemia as a possible cause [12].

Avascular Necrosis (AVN)

Avascular necrosis is commonly associated with corticosteroid treatment used in chemotherapy treatments. The exact pathogenesis is unknown, although several hypotheses have been proposed. The two leading hypotheses include direct vascular damage characterized by a vasculitis process or a gaseous microembolization by corticosteroid hepatopathy [12]. The proximal epiphyses of the femur and humerus are the most commonly involved sites. The explanation for the increased incidence of necrosis in these locations is due to the lack of collateral circuits to compensate for any blood alterations. Figures 30.2 and 30.3 demonstrate osteonecrosis findings typical of AVN.

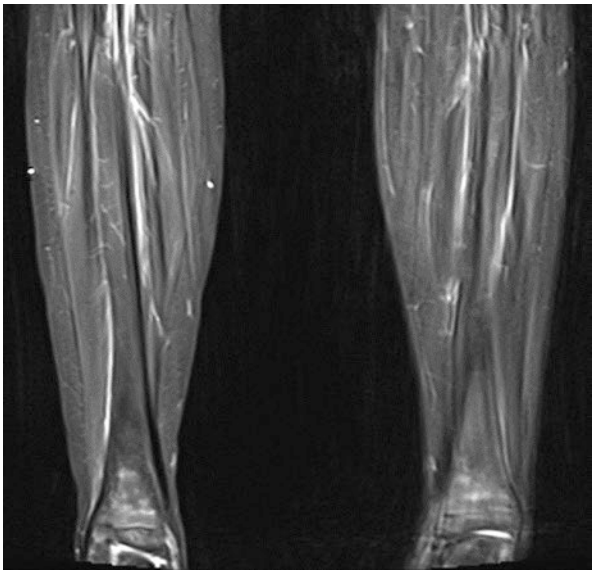


Fig. 30.2 MRI findings of osteonecrosis in distal right tibial and fibular metaphysis with minor osteonecrosis in the left tibia of a 9-year-old male

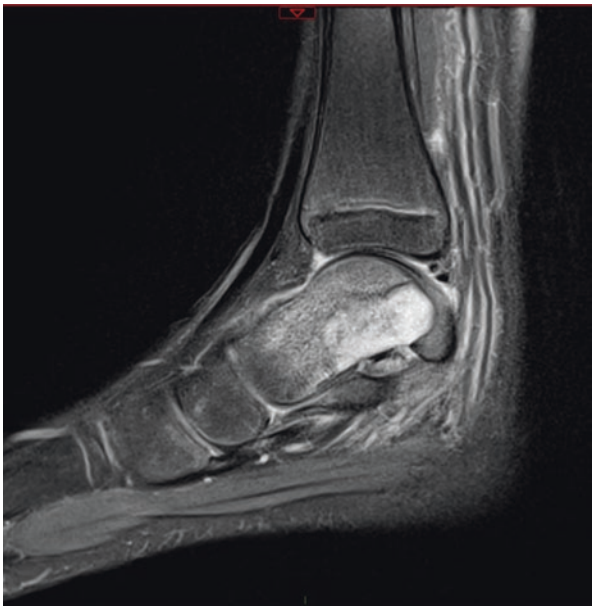


Fig. 30.3 MRI findings of a large focal lesion of subacute osteonecrosis and bone infarct in posteromedial talus with resultant surrounding marrow and tissue edema in 8-year-old male

Conclusion

Despite the many advancements made in the diagnosis, treatment, and prognosis of leukemia in children, there are still areas to explore to improve these measures. Orthopedic providers can provide great support in the earlier diagnosis of leukemia as they become more familiar with its common musculoskeletal and radiographic abnormalities and have a higher index of suspicion of leukemia. This chapter has provided an overview of those common musculoskeletal findings and radiographic abnormalities.

References

1. Ward E, Desantis C, Robbins A, Kohler B, Jemal A. Childhood and adolescent cancer statistics, 2014. CA Cancer J Clin. 2014;64(2):83–103.
2. Hutter JJ. Childhood leukemia. Pediatr Rev. 2010;31(6):234. LP-241.
3. Sinigaglia R, Gigante C, Bisinella G, Varotto S, Zanesco L, Turra S. Musculoskeletal manifestations in pediatric acute leukemia. J Pediatr Orthop. 2008;28(1):20–8.
4. Sharma R, Nalepa G. Evaluation and management of chronic pancytopenia. Pediatr Rev. 2016;37(3):101–13.
5. Pui C-H, Robison LL, Look T. Seminar acute lymphoblastic leukaemia. Lancet. 2008;371:1030–43.
6. Mulder H, Herregods N, Mondelaers V. Musculoskeletal manifestations in children with acute lymphoblastic leukaemia. Belg J Hematol. 2012;3(1):3–11.

7. Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, et al. WHO classification of tumours of haematopoietic and lymphoid tissues. In World Health Organization classification of tumours of haematopoietic and lymphoid tissue, Lyon, France, vol. 4. 2008. 326p.
8. Pui C-H, Evans WE. Treatment of acute lymphoblastic leukemia. N Engl J Med. 2006;354(2):166–78.
9. Hunger SP, Loh ML, Whitlock JA, Winick NJ, Carroll WL, Devidas M, et al. Children's Oncology Group's 2013 blueprint for research: acute lymphoblastic leukemia. Pediatr Blood Cancer. 2013;60:957–63.
10. Gamis AS, Alonzo TA, Perentesis JP, Meshinchi S. Children's Oncology Group's 2013 blueprint for research: acute myeloid leukemia. Pediatr Blood Cancer. 2013;60:964–71.
11. Chell J, Fernandes JA, Bell MJ. The orthopaedic presentation of acute leukaemia in childhood. Ann R Coll Surg Engl. 2001;83(3):186–9.
12. Riccio I, Marcarelli M, Del Regno N, Fusco C, Di Martino M, Savarese R, et al. Musculoskeletal problems in pediatric acute leukemia. J Pediatr Orthop Part B. 2013;22(3):264–9.
13. Maman E, Steinberg DM, Stark B, Izraeli S, Wientroub S. Acute lymphoblastic leukemia in children: correlation of musculoskeletal manifestations and immunophenotypes. J Child Orthop. 2007;1(1):63–8.
14. Jones OY, Spencer CH, Bowyer SL, Dent PB, Gottlieb BS, Rabinovich CE. A multicenter case-control study on predictive factors distinguishing childhood leukemia from juvenile rheumatoid arthritis. Pediatrics. 2006;117(5):e840–4.
15. Kao KL, Hung GY, Hwang B. Pyomyositis during induction chemotherapy for acute lymphoblastic leukemia. J Chinese Med Assoc. 2006;69(4):184–8.
16. Falagas ME, Rafailidis PI, Kapaskelis A, Peppas G. Pyomyositis associated with hematological malignancy: case report and review of the literature. Int J Infect Dis. 2008;12(2):120–5.

Chapter 31
Orthopaedic Manifestations of Hematologic Disorders: Sickle Cell Disease and Hemophilia

Rebecca L. Carl

Sickle Cell Disease

Sickle cell disease (SCD) can manifest in many different ways. Even patients with the same genotype exhibit vast differences in clinical presentation. All forms of SCD involve abnormalities in the beta-globin gene. Red blood cells with abnormal hemoglobin (hemoglobin S) form an abnormal "sickle" shape in response to hypoxia. The sickled cells cause vaso occlusion and subsequent ischemia and tissue damage. Red blood cells with hemoglobin S have a reduced life span, leading to increased turnover and subsequent anemia.

Orthopedic Manifestations of Sickle Cell Disease

Vaso-occlusive Crisis ("Pain Crisis")

Relative hypoxia or inflammation due to factors such as cold, infection, and dehydration leads to sickling of the red blood cells. The sickled cells have a rigid structure and are more likely to stick to the endothelial cells lining blood vessels. The end result of sickling is obstruction of small blood vessels leading to ischemia with tissue damage and pain. In very young infants, the presence of fetal hemoglobin is protective against vaso occlusion. Pain crises typically begin to occur after 6 months of age [1].

R. L. Carl (✉)
Feinberg School of Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL, USA
e-mail: rcarl@luriechildrens.org

J. F. Sarwark, R. L. Carl (eds.), *Orthopaedics for the Newborn and Young Child*,
https://doi.org/10.1007/978-3-031-11136-5_31

In the first years of life, vaso-occlusive crises often involve the hands and feet. This form of pain crisis, known as dactylitis, leads to pain and fusiform swelling of digits. Radiographs show cortical damage and eventual periosteal reaction as new bone forms [2].

Avascular Necrosis (AVN)

Vaso occlusion involving bone leads to avascular necrosis (osteonecrosis). Subchondral avascular necrosis of the epiphysis can cause joint damage and early arthritis. The hip is the most commonly affected joint. Osteonecrosis of the femoral head causes flattening of the femoral head and poor congruence with the acetabulum. Bony infarction in the long bones can also lead to growth disturbances. Avascular necrosis is rare before school-age [1].

Osteomyelitis and Septic Arthritis

Children with SCD have an increased risk of osteomyelitis and septic arthritis. Because children with SCD have splenic infarcts leading to asplenia, they have an increased risk of infection with particular pathogens, including streptococcus pneumoniae, Hemophilus influenza, salmonella, and staphylococcus aureus [3]. Staphylococcus aureus and salmonella strains are the most common causative organisms for osteomyelitis and septic arthritis in individuals with SCD [1].

Because the bone and joint infections can present in a similar manner to pain crises, medical providers need to consider the possibility of infection in infants in children who present with pain involving the extremities. Patients with infection are more likely to have systemic symptoms including lethargy and fever though these features are not specific. With vaso-occlusive crisis, the onset of pain tends to be subtle, while children with osteomyelitis often have a more gradual onset of pain.

In the United States, infants are screened for sickle cell disease as part of the newborn screening program in each state. Early identification of infants with sickle cell allows for antibiotic prophylaxis with penicillin and increased vigilance for infection and appears to lower the risk of infection and morbidity associated with infection.

Hemophilia A and B

Hemophilia A is a genetic disorder that leads to deficiency in factor VIII. Hemophilia B (Christmas disease) involves deficiency of factor IX. Hemophilia A and B occur via an x-linked inheritance pattern. Deficiency of factor VIII or IX leads to

disruption of the clotting cascade and resultant bleeding episodes. The clinical presentation varies based on the levels of factor produced. The practice of prophylactically treating individuals with hemophilia with factor infusions has led to a decrease in the complications associated with these disorders and increase in life expectancy [4, 5]. Factor made with recombinant DNA techniques has attenuated the risk of infection transmission from factor infusion [6].

Children with hemophilia generally have their first bleeding episode before age 2; those with severe hemophilia typically experience bleeding before age 1 [7].

With mild forms of hemophilia, children tend to develop bleeding after moderate to severe trauma. Children with more severe hemophilia may have spontaneous bleeding episodes.

Orthopedic Manifestations of Hemophilia

Hemarthrosis (Joint Bleeding)

Approximately one-quarter of children who present with bleeding episodes in the first 1–2 years of life will have an episode of joint bleeding [7]. Bleeding into the joint space causes expansion of the joint capsule. Infants with hemarthrosis exhibit fussiness and pseudoparalysis as they seek to avoid use of the affected limb. Older children often have some stiffness initially and subsequently develop pain, joint swelling, and limp or refusal to bear weight (when a lower extremity joint is involved). In ambulatory children, the knees and ankles are most likely to be affected. Hemarthrosis involving the elbow is also common.

Muscle Hematoma

Bleeding can also occur in the muscles leading to pain and dysfunction [4, 7]. Severe bleeding can put children at risk for compartment syndrome. Therefore, a child with hemophilia who exhibits signs and symptoms of muscle hematoma, including increasing pain and decreased use of the affected limb, should be evaluated promptly. The classic "P" signs of paresthesia, paralysis, pallor, and pulselessness may be late findings of compartment syndrome; the absence of these features should not be used to rule out possible compartment syndrome.

Hemophilic Arthropathy

Frequent bleeding into the joint can cause chronic damage to the joint. This condition is referred to as hemophilic arthropathy. Hemophilic arthropathy is a late finding, typically seen in adolescence or adulthood. As prophylactic treatment with

recombinant factor has become the standard of care, the rates of hemophilic arthropathy have started to decline [6, 8].

References

1. Vanderhave KL, Perkins CA, Scannell B, Brighton BK. Orthopaedic manifestations of sickle cell disease. J Am Acad Orthop Surg. 2018;26(3):94–101.
2. Almeida A, Roberts I. Bone involvement in sickle cell disease. Br J Haematol. 2005;129(4):482–90.
3. Battersby AJ, Knox-Macaulay HH, Carrol ED. Susceptibility to invasive bacterial infections in children with sickle cell disease. Pediatr Blood Cancer. 2010;55(3):401–6.
4. De Podesta HD, Ono F, De Oliveira GB, et al. Orthopaedic evaluation in children with severe haemophilia A or B submitted to primary prophylaxis therapy in a coagulopathy treatment centre. Haemophilia. 2011;17(2):228–32.
5. Astermark J, Petrini P, Tengborn L, Schulman S, Ljung R, Berntorp E. Primary prophylaxis in severe haemophilia should be started at an early age but can be individualized. Br J Haematol. 1999;105(4):1109–13.
6. Fischer K, Kulkarni R, Nolan B, et al. Recombinant factor IX Fc fusion protein in children with haemophilia B (Kids B-LONG): results from a multicentre, non-randomised phase 3 study. Lancet Haematol. 2017;4(2):e75–82.
7. Kulkarni R, Presley RJ, Lusher JM, et al. Complications of haemophilia in babies (first two years of life): a report from the Centers for Disease Control and Prevention Universal Data Collection System. Haemophilia. 2017;23(2):207–14.
8. Tobase P, Lane H, Siddiqi AE, Ingram-Rich R, Ward RS. Declining trends in invasive orthopedic interventions for people with hemophilia enrolled in the Universal Data Collection program (2000-2010). Haemophilia. 2016;22(4):604–14.

Chapter 32
Langerhans Cell Histiocytosis

Kyle L. MacQuarrie

Brief Overview

Langerhans cell histiocytosis (LCH) is a rare disorder primarily seen in children that is characterized by the proliferation of cells from the myeloid lineage that resemble Langerhans cells—dendritic cells normally found in the skin and mucous membranes. The pathologic accumulation of cells can affect one (single system) or multiple (multisystem) organ systems, with a long-term prognosis that varies depending both on the extent of involvement and the specific affected sites. Bone is the most affected site in children, typically presenting with lytic lesions visible in imaging studies, but skin, spleen, the bone marrow, and other sites can also be involved. Diagnosis can be difficult, given the great variety of ways that the disorder can present, but bony pain, rashes that do not respond to typical treatments, and cytopenias are all potential indicators. Management of the disorder depends both on the number and type of sites involved and can range from observation in some cases, to approaches including surgery and chemotherapy. While the prognosis for limited disease is excellent, there is not insubstantial mortality rate associated with more systemic disease. In addition, bony disease in certain locations puts patients at risk for serious morbidities, most notably that of diabetes insipidus.

K. L. MacQuarrie (✉)
Department of Pediatrics, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA
e-mail: kmacquarrie@luriechildrens.org

J. F. Sarwark, R. L. Carl (eds.), *Orthopaedics for the Newborn and Young Child*,
https://doi.org/10.1007/978-3-031-11136-5_32

Background

LCH is one of the histiocytic disorders, rare disease entities that are characterized by an increased, pathologic abundance of cells from the dendritic, monocytic, and macrophage lineages. Among these disorders—which also include such diagnoses as hemophagocytic lymphohistiocytosis (HLH), macrophage activation syndrome (MAS), and Rosai-Dorfman disease—LCH is the most common. LCH was formerly known as "histiocytosis X," but as more information has been gathered about its underlying biology, especially on a molecular level, it has been reclassified and renamed. LCH is found more often in pediatric populations, though it can affect adults as well, with an incidence estimated to be between 2 and 9 cases per million children per year. The exact incidence has been difficult to establish and is still unclear, as the disease is known to occasionally spontaneously regress, and most epidemiologic studies have been in smaller, geographically restricted cohorts. Both male and female children can be affected, and only relatively small effects of gender on incidence have been described. In children, the greatest incidence is in infants less than 1 year of age, with a decreasing incidence as children age, but the median age of onset is approximately 3.5 years old [1].

The precise pathophysiology of LCH has long been a puzzle, with a great deal of attention given to whether its nature is fundamentally that of a neoplastic disorder, or one solely of immune dysregulation. The lesions of LCH demonstrate the presence of cells with the morphologic and immunophenotypic features of the eponymous Langerhans cells, accompanied by a multitude of other inflammatory cells. It has been shown that the pathologic cells in LCH undergo clonal expansion in the involved tissues, but they have also been shown to release a variety of pro-inflammatory cytokines into the surrounding area [2–4]. These lesions can present in nearly any organ system, with manifestations and characteristics that vary depending on the exact organ involvement (see Table 32.1). More recently, studies have shown a high prevalence of activation of the MAPK (MAP kinase) signaling pathway in LCH, whether through the well-described BRAFV600E mutation [5], or other mutations elsewhere in the signaling cascade that result in activation [6–9]. Activation of this signaling cascade can affect cellular proliferation, differentiation, and apoptosis, providing a potential mechanistic explanation for the pathologic behavior of the cells in LCH lesions. Such mutations lend credence to the model of LCH as a neoplastic disorder that possesses characteristics of immune dysregulation.

Table 32.1 Sites and characteristics of LCH organ involvement at diagnosis [1, 10, 11]

Anatomic site	Prevalence	Risk organ?	Notes
Skeletal bones	80%	No[a]	
Skull	50%		Association with DI (diabetes insipidus)
Pelvis	25%		
Femur	17%		
Ribs	8%		
Skin	30–50%	No	Can manifest as multiple rash types
Lymph nodes	30%	No	Lymphadenopathy on exam, widened mediastinum on chest X-ray if mediastinal node involvement
Lungs	20–40%	No[b]	May require dedicated CT imaging to characterize involvement
Spleen	15%	Yes	Splenomegaly on exam
Liver	15%	Yes	Hepatomegaly on exam, liver dysfunction on labs
Bone marrow	15–30%	Yes	May demonstrate cytopenias on CBC

[a]Some sites of bony disease, such as vertebral and certain craniofacial lesions, impart risks related to their anatomic location and are treated differently than other bony lesions
[b]Previously denoted as a "risk organ"

Clinical Presentation: History and Physical

LCH exhibits a highly variable clinical picture—as well as a highly variable clinical course—and its initial presentation will therefore be dependent on the involved site(s) and extent of disease. Bony lesions and skin lesions are the most common involved systems and are therefore the systems most likely to exhibit a finding on a physical exam or one that is mentioned while gathering a history. For LCH that involves a bony site, local symptoms such as swelling and pain will be most typical, though it is possible for a bony site to be asymptomatic as well. Skin involvement will typically result in a rash, but the appearance and characteristics of the rash can be widely variable. Classic skin presentations include a rash involving the scalp that mimics seborrheic dermatitis and rashes in the diaper area that appear similar to dermatitis (though one that is resistant to typical treatments). However, many other rashes have been described, including those characterized by either hyperpigmented or hypopigmented skin changes, macules, papules, vesicles, and scaling.

Given the possibility for LCH to involve other systems besides skin and bones, as well as the possibility of multiorgan system involvement, the initial history and physical must include an assessment for other sites of involvement. The history should include a thorough review of systems, covering symptoms including fever, fatigue, otorrhea, respiratory changes, polyuria, polydipsia, pain, swelling, lymphadenopathy, unusual bleeding, recurrent infections, and abnormal skin findings. If LCH is suspected at all, physical examination should focus on recognizing accompanying physical findings for organ system involvement. Involvement of lymph nodes, the spleen, or liver is accompanied by lymphadenopathy, splenomegaly, and hepatomegaly, respectively.

Evaluation

If concern for a bony process leads to imaging, standard X-rays are an appropriate initial modality to identify and characterize the lesions. The bony lesions of LCH will often demonstrate an osteolytic appearance, though some variation can exist. Unless there are other items on the physical exam or history that lead to the likely diagnosis of LCH, the initial differential diagnosis for an osteolytic bony lesion may be broad, including numerous items both malignant and non-malignant in nature (see Table 32.2).

While some LCH lesions will exhibit well-circumscribed and smooth edges on imaging, others will have more ragged appearing edges. It has been speculated that those with smooth edges represent older or more advanced lesions. Newer lesions, possessing a more active or ongoing osteolytic process, will appear more "moth-eaten" compared to older lesions [10].

After identification of one or more findings concerning LCH, further evaluation must be focused on (1) confirming the diagnosis and (2) determining the extent of involvement. Fully characterizing the extent of involvement is critical, as treatment and prognosis are both related to an extent. For diagnosis, the gold standard approach is to utilize both histologic and immunophenotypic confirmation from a biopsied lesion. In the rare situations in which a biopsy is impossible to safely acquire (such as for vertebral lesions in the cervical vertebrae), then diagnosis based on radiologic characteristics and exam findings is acceptable. Biopsied material is examined both for the characteristic gross morphologic features of LCH, as well as characteristic cell surface markers.

Under light microscopy, LCH lesions contain scattered large histiocytes with a distinct "coffee bean" nucleus (i.e., a nucleus that has a characteristic groove visible in it). Along with the eponymous histiocytes, there is typically a mixed infiltrate of inflammatory cells, including lymphocytes, eosinophils, and macrophages. On the molecular level, LCH is characterized by immunopositivity for the cell surface marker CD1a, as well as for the marker CD207. Historically, the gold standard of diagnosis included the use of electron microscopy, which had the capability to demonstrate the presence of Birbeck granules in the Langerhans cells. Birbeck granules have a classic "tennis-racket" appearance and are structures that are unique to the cytoplasm of Langerhans cells. However, electron microscopy is no longer required, as CD207 expression has been shown to have an excellent correlation with the presence of Birbeck granules, and can thus substitute for the more labor-intensive and technically challenging technique of electron microscopy [17].

Workup to determine the extent of involvement should involve a skeletal survey, to determine the presence or absence of bony involvement, as well as determining its extent. A chest X-ray should be performed, which serves multiple purposes: to look for bony lesions, to look for evidence of involvement of

Table 32.2 Differential diagnosis and incidence of osteolytic bony lesions [10, 12–16]

Diagnosis	Estimated incidence (per million person-years)[a]
Osteomyelitis	88
Leukemia	40–50
Osteochondroma	35
LCH (Langerhans cell histiocytosis)	2–9
Neuroblastoma	7.5–8.5
Osteosarcoma	4.5–5.5
Rhabdomyosarcoma	4–5.5
Osteoid osteoma	4.5
Fibrous dysplasia	4.5
Retinoblastoma	3–3.3
Bone cyst (simple or aneurysmal)	3 (simple), 5.5 (aneurysmal)
Ewings sarcoma	2.5–3.5
Osteoblastoma	1.2
CRMO (Chronic recurrent multifocal osteomyelitis)	1–2
JXG (Juvenile xanthogranulomatosis)	<1–1.5

[a]Incidence for malignancies refers to overall incidence, not just presentations with bony lesions

mediastinal/perihilar lymph nodes, and to look for pulmonary parenchymal involvement. PET scans are sometimes used to both detect lesions as well as monitor them over time and they have been shown to be more sensitive to changes than other modalities [18].

Management

Treatment of LCH is highly variable, depending on the site(s) of involvement. If there is involvement of multiple organ systems, or risk of organ involvement (bone marrow, spleen, and liver, as noted in Table 32.1), then systemic treatment is the standard approach. In contrast, treatment of single-site involvement does not necessarily require systemic treatment. Studies of treatment regimen duration have shown that therapy that continues on for a full 12 months results in a superior outcome, with lower rates of disease reactivation, compared to therapy of only 6 months' duration [19]. In the cases where risk organs are involved, a longer therapy duration is also recommended to minimize the chance of reactivation and potential long-term morbidities. One of the most well-known and well-described morbidities is that of endocrinopathies such as diabetes insipidus manifesting in patients with cranial bony disease.

Unifocal Bony Disease

In the case of single bony lesions—the most predominant presentation overall of LCH—a spontaneous regression of the lesion may occur. However, given the recommendation that a suspected diagnosis of LCH is confirmed with the examination of a biopsy sample, simple curettage of smaller lesions is often done at the time of biopsy, but its use is highly dependent on the size of the lesion. It is thought that curettage improves resolution and healing of lesions <2 cm, but excision or curettage of those that are >5 cm is not recommended, due to the risk for resultant bony deformities and lengthy recovery time. Lesions that are between 2 and 5 cm may also have a simple curettage performed at the time of biopsy, though the decision is dependent on multiple factors, including the lesion's location and exact size. Additional measures beyond curettage have included intra-lesional injections of steroids, observation, radiation therapy, and systemic therapy. The exact choice of treatment depends on multiple factors and must be determined individually for each case.

Multifocal Bony Disease

Patients who present with LCH involvement restricted to the bones, but with involvement of multiple skeletal sites, are at greater risk of long-term morbidities than those patients who have unifocal bony disease. Given this risk, systemic therapy is often initiated (as described below). Fortunately, the survival rate for multifocal, bone-restricted disease is close to 100%. Given the excellent survival rates, the relative risks and benefits of systemic treatment have to be considered individually in each situation of multifocal bony disease, to determine if a more conservative approach is warranted instead.

Systemic Treatment

Current standard systemic treatment involves the using a combination of a steroid (typically prednisone) with the chemotherapeutic agent vinblastine, one of the vinca alkaloids. This combination therapy is initially given for 6 weeks, with a reassessment for disease response occurring at the end of this time. Depending on response and the presence or absence of risk organ lesions, the same therapy course may instead be extended to 12 weeks of treatment. If there is a complete disease response after that initial 6- or 12-week period of combination therapy, then patients are put on a "maintenance" therapy regimen. The maintenance regimen is given to complete a full year of treatment and typically comprises a more intermittent administration of the steroids and alkaloid agent, along with an oral chemotherapeutic agent

Table 32.3 Outcomes of LCH based on disease extent and location [19, 22]

	Survival	Reactivation/recurrence
Single site disease	~100%	<20%
Multifocal disease		
No risk organ involvement	>95%	30–40%
Risk organ involvement	80–90%[a]	25–30%

[a]Survival drops to ~50% if poor response to initial therapy

(See the Langerhans cell histiocytosis Evaluation and Treatment Guidelines, Histiocyte Society [20]).

Some patients do not respond adequately to the initial course of therapy. Such poor response can include lesions that do not change after the initial course, apparent worsening of lesions, or even the appearance of new lesions. For such patients, "salvage" treatment regimens are utilized. Salvage regimens are more intensive than the initial therapy courses, and often involve chemotherapeutic agents not used in the front-line regimens, resulting in more bone marrow suppression and side effects than that seen with the initial treatments. More recently, with the recognition of the BRAFV600E and other cell signaling pathway mutations, the use of molecular targeted therapies is being investigated in patients. However, those alterations are recent discoveries, and the most efficacious and safest way to use targeted therapies is still unclear (see Table 32.3).

Orthopedic Sequelae and Management

While LCH as a whole has high survival rates, long-term studies have demonstrated a significant burden of permanent sequelae. Studies have estimated the proportion of survivors that have at least one "permanent consequence" to be in the range of 30–70%, with a notable increase in the occurrence of sequelae in those patients who had multisystem disease compared to those with single-system disease. In the case of bony disease, involvement of (1) vertebrae and (2) craniofacial bones deserve special attention. Vertebral involvement by LCH can result in compression of the vertebral body. While over the long-term this issue can largely resolve on imaging, it still puts affected children at risk for scoliosis and requires dedicated monitoring for that issue. It is recommended that such monitoring occur yearly to detect any such issues and address them early. Annual monitoring is also recommended for children with a history of involvement in the craniofacial bones and jaw, as facial asymmetry and jaw growth can be compromised in such cases [11].

Craniofacial involvement, especially if it involves any soft tissue extension into the dura, puts children at risk for two other potential morbidities: (1) diabetes insipidus (DI) and (2) neurologic issues. DI is a well-described risk of LCH, with an overall prevalence of 20–40%, but a higher rate of occurrence in those patients with multisystem disease. DI is not just a late effect of disease; it may be present at

diagnosis or develop in the weeks to months after diagnosis is established. Neurologic issues occur in approximately 10% of cases of those patients with craniofacial involvement. The exact manifestations vary between patients but can include neurocognitive deficits, cerebellar dysfunction, and seizures. The "neurologic issues" category of late effects is less likely to be seen up front or early in the disease course when compared to DI and is more likely to be identified significantly later after diagnosis [21].

Clinical Pearls

- LCH should be considered in the differential of osteolytic skeletal lesions, especially those present in the skull.
- Rashes such as seborrheic dermatitis or diaper dermatitis that do not respond to typical treatments may represent the skin manifestation of LCH.
- There is a significant association between diabetes insipidus and craniofacial bony involvement of LCH.
- LCH treatment is highly variable, depending on the exact location and extent of organ involvement, and is therefore best handled by specialists and centers with experience in this rare disease.

Resources

Website of the Histiocyte Society (an international organization of medical professionals focused on improving care and research regarding histiocyte disorders): https://histiocytesociety.org/.

Website of the Histiocytosis Association (an international nonprofit organization that focuses on funding histiocytosis research, awareness and education initiatives, and patient/family support): https://www.histio.org/.

References

1. Guyot-Goubin A, Donadieu J, Barkaoui M, Bellec S, Thomas C, Clavel J. Descriptive epidemiology of childhood Langerhans cell histiocytosis in France, 2000–2004. Pediatr Blood Cancer. 2008;51(1):71–5.
2. Yu RC, Chu AC, Chu C, Buluwela L. Clonal proliferation of Langerhans cells in Langerhans cell histiocytosis. Lancet. 1994;343(8900):767–8.
3. Willman CL, Busque L, Griffith BB, Favara BE, McClain KL, Duncan MH, et al. Langerhans'-cell histiocytosis (histiocytosis X)—a clonal proliferative disease. N Engl J Med. 1994;331(3):154–60.

4. Egeler RM, Favara BE, van Meurs M, Laman JD, Claassen E. Differential In situ cytokine profiles of Langerhans-like cells and T cells in Langerhans cell histiocytosis: abundant expression of cytokines relevant to disease and treatment. Blood. 1999;94(12):4195–201.
5. Badalian-Very G, Vergilio J-A, Degar BA, MacConaill LE, Brandner B, Calicchio ML, et al. Recurrent BRAF mutations in Langerhans cell histiocytosis. Blood. 2010;116(11):1919–23.
6. Diamond EL, Durham BH, Haroche J, Yao Z, Ma J, Parikh SA, et al. Diverse and Targetable Kinase Alterations Drive Histiocytic Neoplasms. Cancer Discov. 2016;6(2):154–65.
7. Nelson DS, van Halteren A, Quispel WT, Van den Bos C, Bovée JVMG, Patel B, et al. MAP 2K1and MAP 3K1mutations in langerhans cell histiocytosis. Genes Chromosomes Cancer. 2015;54(6):361–8.
8. Brown NA, Furtado LV, Betz BL, Kiel MJ, Weigelin HC, Lim MS, et al. High prevalence of somatic MAP 2K1 mutations in BRAF V600E–negative Langerhans cell histiocytosis. Blood. 2014;124(10):1655–8.
9. Chakraborty R, Hampton OA, Shen X, Simko SJ, Shih A, Abhyankar H, et al. Mutually exclusive recurrent somatic mutations in MAP 2K1 and BRAF support a central role for ERK activation in LCH pathogenesis. Blood. 2014;124(19):3007–15.
10. Khung S, Budzik J-F, Amzallag-Bellenger E, Lambilliote A, Soto Ares G, Cotten A, et al. Skeletal involvement in Langerhans cell histiocytosis. Insights Imaging. 2013;4(5):569–79.
11. Haupt R, Minkov M, Astigarraga I, Schäfer E, Nanduri V, Jubran R, et al. Langerhans cell histiocytosis (LCH): guidelines for diagnosis, clinical work-up, and treatment for patients till the age of 18 years. Pediatr Blood Cancer. 2012;60(2):175–84.
12. American Cancer Society. Cancer facts & figures 2014, special section: cancer in children and adolescents. Atlanta: American Cancer Society; 2014.
13. Kremers HM, Nwojo ME, Ransom JE, Wood-Wentz CM, Melton LJ, Huddleston PM. Trends in the epidemiology of osteomyelitis. J Bone Joint Surg Am. 2015;97(10):837–45.
14. van den Berg H, Kroon HM, Slaar A, Hogendoorn P. Incidence of biopsy-proven bone tumors in children. J Pediatr Orthop. 2008;28(1):29–35.
15. Chun CSY. Chronic recurrent multifocal osteomyelitis of the spine and mandible. Pediatrics. 2004;113(4):380–4.
16. Janssen D, Harms D. Juvenile xanthogranuloma in childhood and adolescence. Am J Surg Pathol. 2005;29(1):21–8.
17. Valladeau J, Ravel O, Dezutter-Dambuyant C, Moore K, Kleijmeer M, Liu Y, et al. Langerin, a novel C-type lectin specific to Langerhans cells, is an endocytic receptor that induces the formation of Birbeck granules. Immunity. 2000;12(1):71–81.
18. Phillips M, Allen C, Gerson P, McClain K. Comparison of FDG-PET scans to conventional radiography and bone scans in management of Langerhans cell histiocytosis. Pediatr Blood Cancer. 2009;52(1):97–101.
19. Gadner H, Minkov M, Grois N, Pötschger U, Thiem E, Aricò M, et al. Therapy prolongation improves outcome in multisystem Langerhans cell histiocytosis. Blood. 2013;121(25):5006–14.
20. Website of the Histiocyte Society (an international organization of medical professionals focused on improving care and research regarding histiocyte disorders). https://histiocytesociety.org/.
21. Haupt R, Nanduri V, Calevo MG, Bernstrand C, Braier JL, Broadbent V, et al. Permanent consequences in Langerhans cell histiocytosis patients: a pilot study from the Histiocyte Society-Late Effects Study Group. Pediatr Blood Cancer. 2004;42(5):438–44.
22. Titgemeyer C, Grois N, Minkov M, Flucher-Wolfram B, Gatterer-Menz I, Gadner H. Pattern and course of single-system disease in Langerhans cell histiocytosis data from the DAL-HX 83- and 90-study. Med Pediatr Oncol. 2001;37(2):108–14.

Chapter 33
Myelomeningocele

Vineeta T. Swaroop

Background

Neural tube defects (NTD) result from failure of the neural tube to close during embryogenesis. While decreased compared to previous decades, the incidence of NTD remains at 2:10,000 live births in the United States [1]. The most common NTD is myelomeningocele (MM), also known as spina bifida, which is a fluid-filled cystic swelling, formed by dura and arachnoid (Fig. 33.1). Myelodysplasia of the neural elements manifests in the vertebrae as a defect in the posterior elements while dysplasia of the spinal cord and nerve roots leads to bowel, bladder, motor, and sensory paralysis below the level of the lesion. Patients with MM may also have concomitant lesions of the spinal cord, such as diastematomyelia or hydromyelia, or structural abnormalities of the brain, such as hydrocephalus or Arnold-Chiari malformation, which can also compromise neurologic function. MM is the most severely disabling birth defect compatible with survival [2].

Due to two important advances in the management of MM, the survival rate into adulthood has improved from 10% in the 1950s to 75–85%, currently [3]. These two advances were the development of effective treatment for hydrocephalus and introduction of clean intermittent catheterization for bladder dysfunction [4]. In order to prevent, monitor, and treat the variety of potential complications that threaten function, quality of life, and survival, comprehensive, multidisciplinary care is ideal for patients with MM. The effective team approach includes orthopedic surgery, neurosurgery, urology, rehabilitation, physical and occupational therapy, and orthotics. In addition, access to nutrition, social work, wound care, and psychology is preferred.

With regard to orthopedic manifestations, both congenital and acquired deformities occur in patients with MM. The goal of orthopedic care is to prevent or correct

V. T. Swaroop (✉)
Department of Orthopaedic Surgery, Ann & Robert H Lurie Children's Hospital of Chicago, Chicago, IL, USA
e-mail: vtswaroop@luriechildrens.org

J. F. Sarwark, R. L. Carl (eds.), *Orthopaedics for the Newborn and Young Child*,
https://doi.org/10.1007/978-3-031-11136-5_33

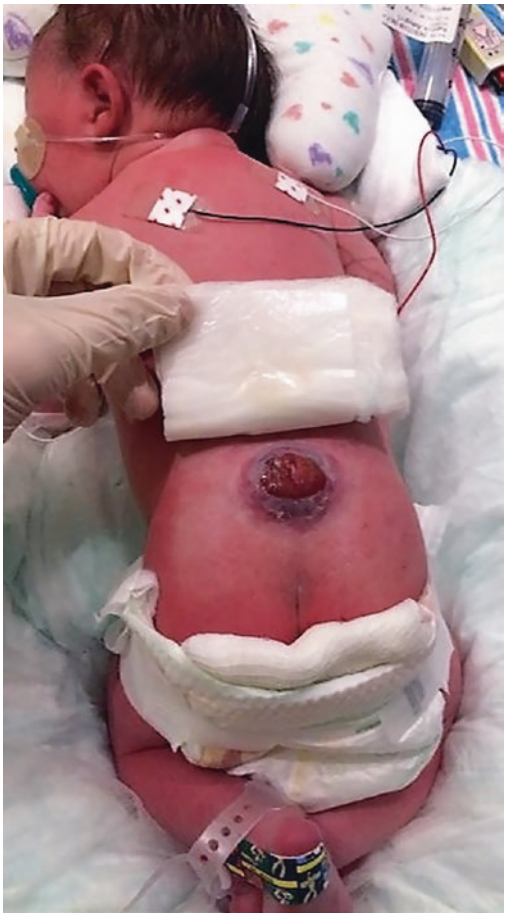


Fig. 33.1 Clinical photograph of a newborn with open myelomeningocele prior to postnatal closure of the defect. Note the lack of skin covering the exposed neural elements

deformities to maximize mobility, function, and independence. The orthopedic surgeon's job is to assist the patient and family in developing realistic goals, individualized to the patient's functional level of involvement, and provide the care necessary to meet these goals. Also important is for providers to help foster intellectual and personality development through early introduction of wheeled mobility, wheelchair sports programs beginning in preschool, and educational mainstreaming, all of which can lead to increased independence [5].

Epidemiology/Pathophysiology

MM results from failure of fusion of the neural folds during neurulation, which occurs during the fourth week of embryogenesis. Neurulation defects are those conditions resulting from abnormalities during the closure of the neural tube including MM and anencephaly. In contrast, postneurulation defects arise from

abnormalities during the canalization phase, from 28 to 48 days of gestation, including meningocele, lipomeningocele, and diastematomyelia. With regard to the neurulation defects, much research has been devoted to determining whether the resulting neurological issues are caused by this primary disorder of neurulation or by secondary damage to the developing spinal cord which is then exposed to the toxic intrauterine environment, or both [6, 7]. This is described by the "two-hit" hypothesis: myelodysplasia occurs from failure of primary neurulation in the embryonic period (first-hit); and secondary acquired damage of neural tissue hence irreversible loss of neurological function occurs from the absence of skin/musculoskeletal coverage exposing the neural tissue to the intrauterine environment (second-hit) [7, 8]. This "two-hit" hypothesis is the driving force for the development of intrauterine MM repair options in hopes of improving neurological outcomes.

The cause of the first-hit, failure of neurulation, is not known but is suspected to be multifactorial, involving both environmental and genetic factors. Many environmental factors have been examined for a potential role in NTDs, including temperature, drug exposure, substance abuse, maternal infection, and nutritional factors such as folate, vitamin B_{12}, and zinc. Multiple studies have established the importance of folic acid (FA) in prevention of NTD, with a 72% protective effect [9, 10]. As a result, the United States Public Health Service recommends all women of childbearing age capable of becoming pregnant should consume 400 μg FA per day to reduce risk of NTDs [11].

Genetic factors also play a role, evidenced by association with less common single gene defects, increased recurrence risk among siblings, and higher frequency in twins. Animal studies have shown as many as 100 mutant genes that affect neurulation, and almost all have homologs in humans [12, 13]. These candidate genes include those that regulate FA, glucose, or retinoid metabolism as well as apoptosis and the planar cell polarity pathway.

Common Clinical Presentation: History and Physical

Orthopedic care of a patient with MM begins either during prenatal consultation, or postnatally in the neonatal intensive care unit. A manual muscle test (MMT) should be performed by a specially trained physical therapist prior to closure of the MM defect in order to determine the neurologic level of function for each limb (Fig. 33.2). After closure, the orthopedic team performs a detailed physical examination of the patient assessing spinal alignment, as well as alignment, range of motion, muscle tone abnormalities, and strength in all four extremities. Skin integrity is also inspected. Providers should pay special attention to evaluating for any associated conditions which may mandate treatment early in the postnatal period, such as kyphosis, clubfoot, vertical talus, or hip or knee contractures. Based on the clinical examination and the results of the MMT, the orthopedist can counsel the family regarding expectations for short- and long-term ambulatory potential as well as anticipated need for orthoses or assistive devices in the future.

Myelomeningocele MMT/ROM
PATIENT: **DATE:**
DIAGNOSIS: Myelomeningocele **DOB:** **PHYSICIAN:**

RANGE OF MOTION°

HIP	RIGHT	LEFT
Flexion		
Abduction (hip extended)		
Adductor stretch reflex		
Abduction (hip flexed)		
Adduction		
Internal/external rotation		
Hip flexion contracture		
Ober test		

KNEE	RIGHT	LEFT
Flexion (prone)		
Flexion (supine)		
Extension		
Straight leg raise		
Popliteal angle (bilateral)		

ANKLE	RIGHT	LEFT
Dorsiflexion (knee flexed)		
Dorsiflexion (knee extended)		
Plantar flexor stretch (R1) (knee flexed/knee extended)		
Clonus (knee flexed/knee extended)		
Plantar flexion		
Thigh-foot angk		
Thigh foot angle range (ext/int)		
Forefoot abd/add		

Ligamentous Laxity	RIGHT	LEFT
Medial coll. (Knee Flexed)		
Medial coll. (Knee extended)		
Lateral coll. (Knee Flexed)		
Lateral coll. (Knee extended)		

WEIGHT BEARING	RIGHT	LEFT
hindfoot valgus		
hindfoot varus		
correctable		
equinus		
correctable		
hallux valgus/varus		
rocker bottom midfoot		

MEASUREMENTS*	RIGHT	LEFT
leg length		
calf circumference		

*in centimeters

STRENGTH

	COMMENTS:	RIGHT CC	RIGHT IP	LEFT CC	LEFT IP
Iliopsoas					
Sartorius					
Gluteus maximus					
Gluteus medius					
Tensor					
Adductors					
Medial humstrings					
Lateral hamstrings					
Quadriceps					
Anterior tibialis					
Posterior tibialis					
Gastroc (hand test)					
Gastroc (standing)					
Soleus					
Peroneus longus					
Brevis					
Toe ext. longus					
Brevis					
Toe flex. longus					
Brevis					
EHL					
EHB					
FHL					
FHB					
Lumbricales					

CC - cerebral control/IP - in pattern

		DEFINITION
X	Present	Unable to be graded, but working
5	Normal	Complete range of motion against gravity with full resistance
4	Good	Complete range of motion against gravity with moderate resistance
4-	Good Minus	Complete range of motion against gravity with some resistance
3+	Fair	Complete range of motion against gravity with slight resistance
3	Fair	Complete range of motion against gravity
3-	Fair Minus	Incomplete (greater than 1/2 way) range of motion against gravity
2+	Poor Plus	Less than 1/2 way against gravity or full ROM with gravity eliminated plus slight resistance
2	Poor	Complete range of motion with gravity eliminated
2-	Poor Minus	Incomplete range of motion with gravity eliminated
1	Trace	Contraction is felt but there is no visible joint movement
0	Zero	No contraction is felt in the muscle

Fig. 33.2 Sample manual muscle test form. Adapted with permission from Motion Analysis Center, Shirley Ryan Ability Lab, Chicago, IL

Radiographic Studies/Testing/Evaluation

One of the most important tests with relevance to orthopedic care of patients with MM is the MMT, described above. The MMT should be performed prior to closure of the open defect for babies undergoing postnatal closure. For babies who have had

prenatal closure, the MMT should be performed within the first 48 h of life whenever possible. In addition, prior to discharge from the hospital, all newborns with MM should have a baseline anteroposterior pelvis radiograph and anteroposterior and lateral views of the entire spine. The pelvis radiograph helps the orthopedist to determine the baseline status of the hips while the spine radiographs should be screened carefully for any concomitant congenital vertebral malformations which may predispose the patient to earlier development of scoliosis. In addition, the spine radiographs may show kyphosis which in some patients may present as a large, rigid curve at the time of birth.

Detailed Description of Condition

The most important factor affecting ambulatory potential of a patient with MM is the neurologic level of involvement. Functional iliopsoas and quadriceps strength have shown a strong correlation with the future ambulatory ability [14, 15]. Many other factors affect whether or not a patient achieves and can maintain the ambulatory potential predicted from muscle strength including impaired balance, spasticity, ventriculoperitoneal shunt (VPS) revisions, presence of a tethered cord, age, obesity, and musculoskeletal conditions including hip contractures, scoliosis, and foot and ankle deformity.

Patients with MM can be classified into four main groups based on the anatomic level of the lesion as well as the associated functional level, determined from the results of the MMT, and ambulatory capability [16, 17] (Table 33.1).

The first group includes patients with thoracic and high-lumbar (L3 or above) level of involvement, approximately 30% of patients with MM. This group is defined by the lack of functional quadriceps activity. Hence, to achieve ambulation during childhood, patients require a walker and hip-spanning bracing with either a reciprocating gait orthosis (RGO) (Fig. 33.3) or a hip-knee-ankle-foot orthosis (HKAFO). The majority of patients in this group require a wheelchair for mobility in adulthood due to both the high energy cost of ambulation and the frequent incidence of scoliosis and hip and knee contractures. Despite this, it has been shown that patients who participated in a walking program early in life were more independent and better able to accomplish independent transfers later in life compared with those who did not achieve early walking [18].

The next group, those with the low-lumbar level of involvement, also includes approximately 30% of patients with MM. Patients in this group have functional (MMT grade ≥ 3) quadriceps and medial hamstring activity but lack functional activity in the gluteal and gastrocsoleus muscles. As a result, patients in this group require ankle-foot orthoses (AFOs) (Fig. 33.4) to control the position of the foot and ankle as well as an assistive device to compensate for the gluteal lurch. Most patients in this group retain the ability for community-level ambulation in adulthood, although many will use a wheelchair for long-distance mobility [17, 19]. Patients with the low-lumbar level of involvement have the most potential benefit from careful orthopedic care for musculoskeletal deformities. Aggressive treatment of hip

Table 33.1 Functional classification of myelomeningocele

Group	Anatomic level of lesion	Prevalence	Function level (from MMT)	Ambulatory capacity
Thoracic/ High lumbar	L2 or above	30%	No functional quadriceps (≤ grade 2)	Ambulation mostly limited to childhood and requires bracing to level of pelvis (RGO, HKAFO)
Low lumbar	L3 to L5	30%	Quadriceps, medial hamstring ≥ grade 3. No functional activity in gluteals, gastrocnemius (≤ grade 2)	Ambulation with AFOs and many require assistive device 80–95% patients maintain community ambulation into adulthood
High sacral	S1 to S3	30%	Quadriceps, gluteus medius ≥ grade 3 No functional activity in gastrocnemius (≤ grade 2)	Ambulation with AFOs 94–100% patients maintain community ambulation into adulthood
Low sacral	S4 to S5	5–10%	Quadriceps, gluteus medius, gastrocnemius ≥ grade 3	Ambulation without orthoses or assistive device 94–100% patients maintain community ambulation into adulthood

RGO reciprocating gait orthosis, *HKAFO* hip-knee-ankle-foot orthosis, *AFO* ankle-foot orthosis

Fig. 33.3 Clinical photograph of a patient with thoracic level of involvement utilizing a reciprocating gait orthosis (RGO) and reverse walker for ambulation

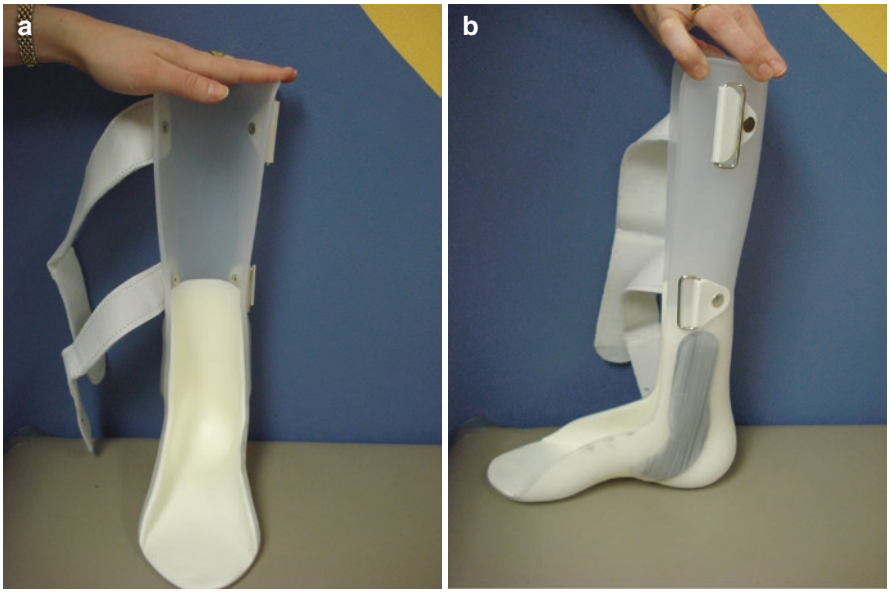


Fig. 33.4 Ankle-foot orthosis (AFO), (**a**) front view and (**b**) side view

contractures, rotational malalignment of the tibia, and deformities of the knee, ankle, and foot are essential to maintain functional ambulation [20, 21].

Patients with sacral level of involvement are divided based on the presence of functional activity in the gastrocsoleus complex. Those with high-sacral level of involvement, approximately 30% of patients with MM, have functional quadriceps and gluteus medius but lack functional activity in the gastrocsoleus. Patients in this group use an AFO but do not require an assistive device. In contrast, patients with low-sacral level of involvement, approximately 5–10% of those with MM, have functional activity in the gastrocsoleus. Patients in this group ambulate with orthoses or assistive devices with a nearly normal gait pattern. Nearly 100% of patients with sacral level of involvement maintain community-level ambulation in adulthood [19, 22, 23]. Aggressive treatment of tethered cord syndrome, avoidance of arthrodesis in the foot, and treatment of knee, ankle, and foot deformities are important in this group to facilitate efficient ambulation.

Treatment/Management

Fetal surgery to perform intrauterine closure of the MM spinal defect is becoming more available after initially being conceived as an attempt to improve neurologic outcomes based on the "two-hit" hypothesis, described above. The current standard of neurosurgical care is the closure of the MM defect within 48–72 h of birth. This

postnatal closure prevents further neurological deterioration but cannot reverse the damage that has already occurred. In contrast, the goal of fetal surgery is to prevent progressive neural tissue destruction and attempt to improve neurologic outcomes at birth. Additionally, in utero repair may stop leakage of cerebrospinal fluid pressure reducing rates of hindbrain herniation and hydrocephalus.

A randomized controlled trial, Management of Myelomeningocele Study (MOMS), was carried out at three American centers between 2003 and 2008. While intending to randomize 200 pregnant women to either intrauterine repair or postnatal closure, the MOMS trial was stopped after 183 patients were enrolled due to the benefits of intrauterine surgery. A report on the initial 158 patients enrolled in MOMS showed significantly decreased rates of VPS placement of 40% in the intrauterine repair group compared to 82% in the postnatal group [24]. The intrauterine repair group was also noted to have improved mental development, motor function at 30 months, and ambulation at 30 months. However, serious complications including higher risk of preterm delivery and uterine dehiscence were reported in the intrauterine repair group. The participating medical centers reported on their continued experience with intrauterine repair after the MOMS trial and noted a decrease in risk with improvements in technique [25].

Based on the available early outcomes data from intrauterine repair, there seems to be a positive effect on lower extremity function, although few studies compare similar groups undergoing prenatal vs postnatal closure. Multiple studies lacking a control group for comparison have reported motor function and ambulatory ability better than what would be predicted from the anatomic level of involvement [25–27]. Early data from the MOMS trial showed patients undergoing prenatal repair were significantly more likely to function two or more levels better than predicted from anatomical level compared to patients undergoing postnatal repair. In addition, those with prenatal repair were less likely to function two or more levels worse than expected and more likely to be able to ambulate without orthotics or assistive devices [24]. Recently 30-month outcomes for the entire cohort of MOMS patients were reported confirming these findings despite a higher level of lesion and increased premature delivery in the prenatal closure group [28].

Regardless of whether the MM defect repair is performed pre- or postnatally, orthopedic care of the newborn with MM begins with a thorough examination in the neonatal intensive care unit, as described above. Prior to discharge from the hospital, orthopedists should provide patients with an order for outpatient physical therapy to focus on a core strengthening program. The most common orthopedic deformities requiring treatment early in the postnatal period are kyphosis, hip or knee contractures, clubfoot, and vertical talus.

Also commonly noted in the postnatal period is paralytic hip subluxation or dislocation, although the recommended management of hip instability in patients with MM has changed dramatically over time. This change in treatment strategy has resulted from an increased emphasis on functional outcomes based on a better appreciation of the effect (or lack thereof) of hip instability on gait through the use of computerized gait analysis [29]. This has led to an understanding that gait symmetry corresponds to the absence of hip contracture, but is not related to hip

subluxation or dislocation. Examination of the functional results of surgical hip reduction shows no improvement in range of motion, ambulatory ability, decrease in pain, or decreased need for bracing. A review of the literature confirms that current treatment goals should focus on maintaining hip range of motion with no role for hip reduction in patients with low-lumbar or higher functional levels of involvement [30]. As such, splinting, bracing, or other treatment for the newborn with hip subluxation or dislocation is unnecessary and not recommended.

Kyphosis, a C-shaped curve in the T2 spine, affects up to 20% of patients with MM. Patients with kyphosis may have a large, rigid curve at birth, often exceeding 80° (Fig. 33.5) [31]. Progression of the curve is related to the level of the neurologic lesion but often occurs rapidly after the first year of life when the child begins to sit

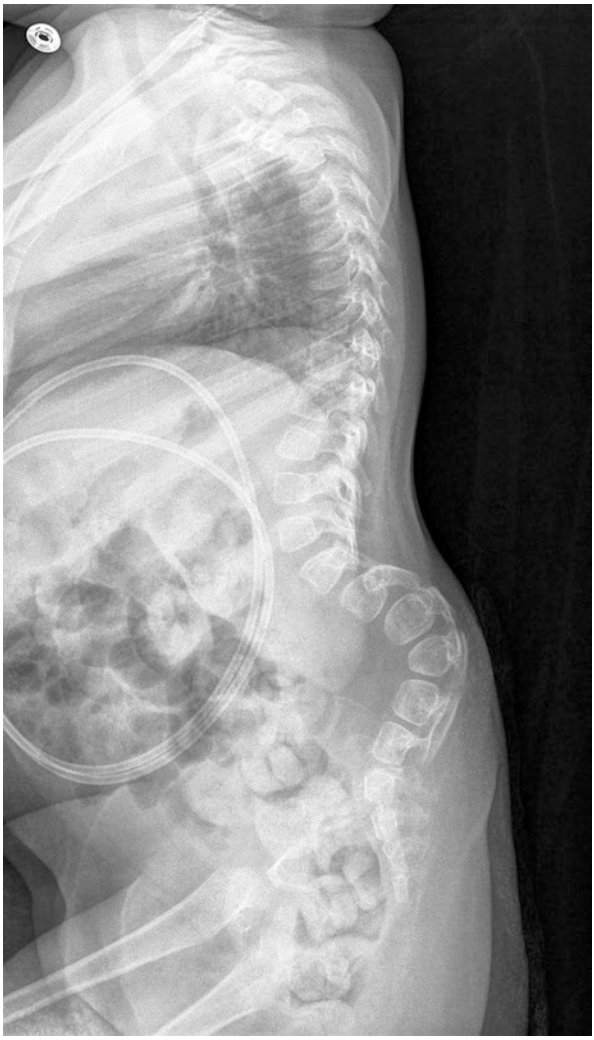


Fig. 33.5 Lateral radiograph demonstrating C-shaped kyphosis in a patient with thoracic level MM

[32]. The kyphotic deformity can cause difficulty with sitting or lying supine as well as problems with skin breakdown over the prominence of the deformity with resulting risk of infection. Nonsurgical treatment with orthoses or modified seating systems has been mostly ineffective. For large, rigid curves, surgical treatment is often indicated to correct sitting posture, prevent skin breakdown, and prevent deformity progression [33].

Hip and/or knee contractures may be present at birth (Fig. 33.6) due to muscle imbalance and in utero positioning. Severe hip flexion contractures may interfere with prone positioning, which is often required postnatally to allow the MM defect to heal. In this case, a modified side-lying position may be necessary. In the majority of patients, hip flexion contractures tend to decrease in the first 2 years of life. When needed, treatment may involve physical therapy, night splinting with a total body splint, or the use of a stander to facilitate hip stretch. Surgical treatment with soft tissue release is rarely indicated.

Knee extension contracture often presents bilaterally and is frequently associated with other congenital anomalies such as hip dislocation, hip contracture, and clubfoot. In most young patients, treatment with serial long leg casting is successful. Casting should be continued until at least 90° of knee flexion is achieved and should be followed by physical therapy and/or night bracing. Surgical treatment is indicated in cases when persistent or recurrent contracture interferes with sitting safely in a car seat, use of a wheelchair, or ability to perform transfers.

The most common orthopedic issue noted in the newborn period is foot deformity. With the exception of clubfoot and vertical talus, many foot deformities presenting in the newborn are flexible or partly flexible and can be treated with gentle stretching often in combination with a low-temperature AFO typically used for 2-h periods at a time. Parents and providers must be vigilant to ensure skin integrity when using an AFO. The more rigid deformities of clubfoot and congenital vertical

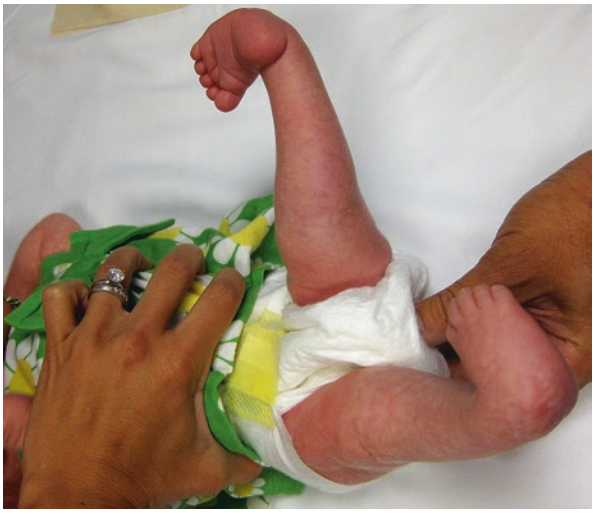


Fig. 33.6 Newborn patient with thoracic level MM with left hip flexion contracture, bilateral knee extension contractures, and bilateral clubfoot

talus require treatment with a careful manipulation and casting program. This may be initiated on an outpatient basis once the patient has been discharged from the hospital. While initial success rates of casting programs are high for both clubfoot and vertical talus, recurrence rates are much higher compared to idiopathic deformities, particularly for clubfoot [34].

Clubfoot is the most common foot deformity seen in patients with MM [31, 35–37]. The incidence of clubfoot correlates with the level of involvement, ranging from up to 90% of patients with thoracic or lumbar levels of involvement to 50% of patients with sacral level involvement [31]. Quite different from idiopathic clubfoot, the clubfoot deformity in patients with MM is notable for severe deformity (Fig. 33.7), marked rigidity, recalcitrance to treatment with higher failure rates, and risk of recurrence [34]. The Ponseti serial casting method is now the standard first-line treatment for patients with an MM-related clubfoot. Many studies have

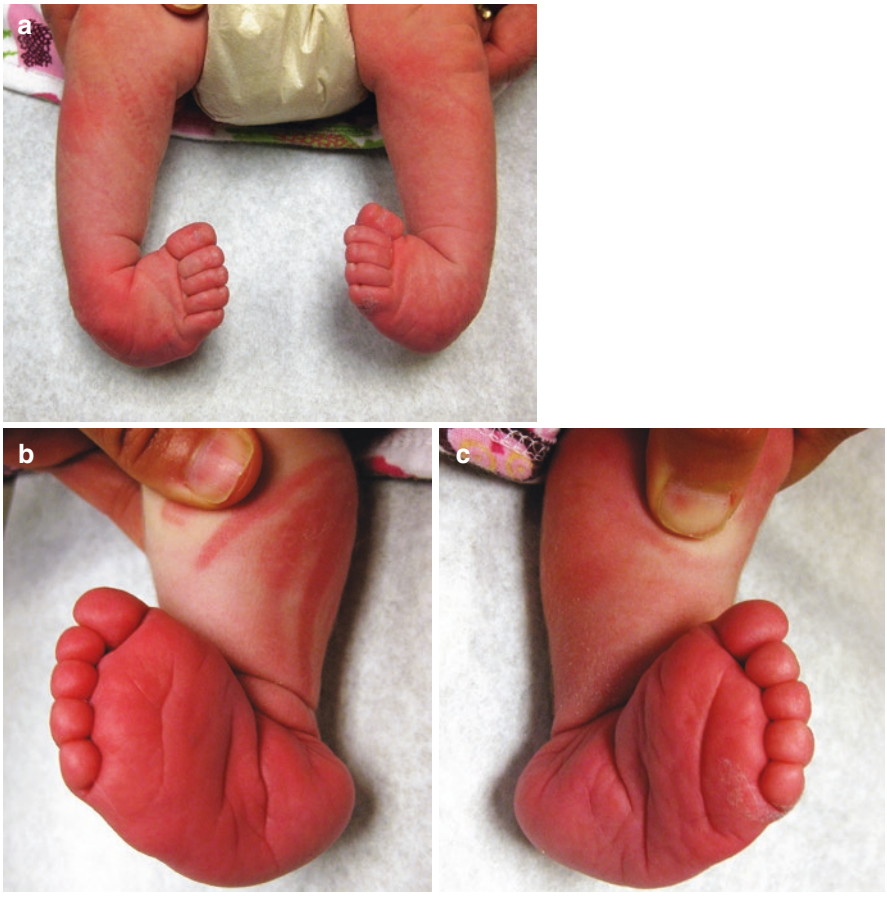


Fig. 33.7 Newborn patient with low-lumbar level MM. (**a**) Bilateral severe, rigid clubfoot deformities. (**b**, **c**) Note the presence of deep posterior and medial creases

demonstrated very high initial rates of successful correction followed by subsequent high risk of recurrence ranging from 56 to 68% [34, 38–40]. Complication rates are also relatively high including skin breakdown, cast slippage, and fracture. Despite this, the Ponseti method has decreased the need for extensive soft tissue release surgery to only 14–33% at short- to mid-term follow-up [34, 38–40]. Prior to initiation of treatment, families should be counseled about realistic expectations with regards to the high risk of recurrence and the potential need for further treatment.

Vertical talus, a rigid, rocker bottom flatfoot deformity (Fig. 33.8), occurs in 10% of patients with MM [21, 37]. Findings include extreme, rigid plantar flexion of the talus in a nearly vertical position (Fig. 33.9) with the talar head palpable in the longitudinal arch of the foot. The talonavicular joint is dislocated dorsolaterally, and the foot is not correctable by manipulation. Similar in theory to the Ponseti method for clubfoot, Dobbs et al. have popularized a minimally invasive manipulation and casting protocol for vertical talus which is followed by a limited open talonavicular joint pinning and Achilles tenotomy [41]. Encouraging short-term results have been reported for patients with vertical talus associated with MM [42–44]. Although long-term results and recurrence rates are not yet established, this method provides a noninvasive option for potentially avoiding the need for extensive soft tissue release surgery.

For those patients without an orthopedic deformity requiring treatment early in the postnatal period, routine orthopedic follow-up should occur every 3–4 months during the first year of life. At approximately 1 year of age, AFOs should be prescribed to compensate for muscle weakness and enable upright mobility. For patients with adequate head and neck control but who are unable to pull to stand at a year of age, a standing frame is often used to facilitate weight bearing and free the child's hands to work on fine motor control. Thereafter, patients are seen every 6 months until the age of 12 and then followed annually. The follow-up periodic

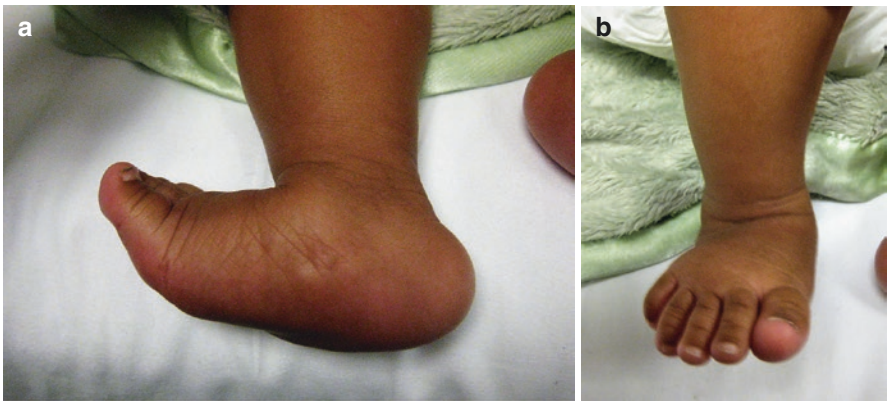


Fig. 33.8 Newborn patient with low-lumbar level MM with vertical talus. Clinical photographs demonstrate (**a**) rigid, rocker bottom foot deformity. The head of the talus is palpable in the longitudinal arch and non-mobile. (**b**) Note anterior crease consistent with dorsolateral dislocation of the talonavicular joint

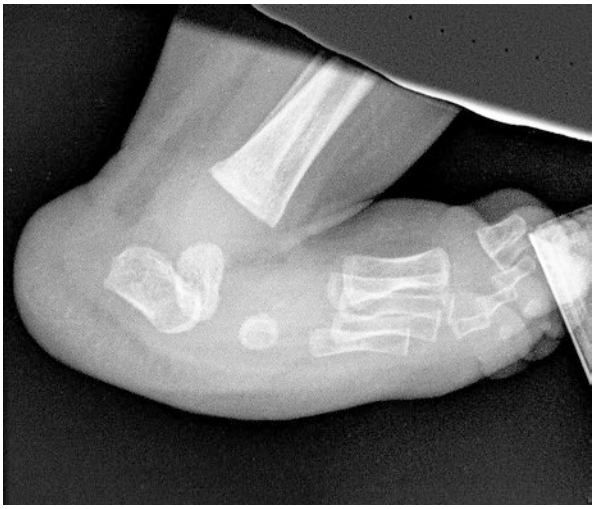


Fig. 33.9 Lateral radiograph of foot with vertical talus showing extreme, rigid plantar flexion of the talus with dorsolateral dislocation of the talonavicular joint

orthopedic examination should include a detailed, systematic assessment and monitoring of motor and sensory function. In addition, each visit should include evaluation of gait, spinal and lower extremity alignment, and skin integrity. Orthoses should be inspected on a regular basis to ensure appropriate fit with no skin irritation. An MMT should be performed at least annually. Range of motion and alignment should be noted over time, and any changes that negatively affect function should be addressed. The provider should always be monitoring for common signs of tethered cord syndrome, such as progressive scoliosis, gait changes, loss of muscle strength, spasticity, back pain, or changes in urologic function [3, 45]. Since patients with MM have multiple medical comorbidities that can affect orthopedic treatment, ideally care should be administered as part of a multidisciplinary team including neurosurgery, urology, and physiatry.

Clinical Pearls

- Skin breakdown is a significant problem in patients with MM who lack protective sensation. To prevent the development of pressure sores, patients should be instructed from a young age to perform daily skin checks, avoid walking on rough or hot surfaces without adequate foot protection, wear water socks or shoes when swimming in pools, and proactively guard against burns (e.g., from bathwater or heat source (radiator) next to bed).
- Fractures occur in up to 40% of patients with MM, who are at known risk for osteopenia, and may result from minor trauma or physical therapy [46]. Since patients with MM may not have pain, caregivers should have a high index of suspicion when any patient presents with a warm, erythematous, swollen extrem-

ity. This is worrisome for a fracture until proven otherwise and radiographs should always be obtained. Typical presentation of a fracture in MM may also include fever, leukocytosis, or elevated erythrocyte sedimentation rate. If not aware of this characteristic presentation for fracture, a mistaken diagnosis of cellulitis may be made and delay proper treatment. Since bone mineral density has been shown to be reduced in partial- and non-ambulators [47], these patients should be monitored closely from an early age to determine who would benefit from a directed bone health program.

- Childhood obesity affects 40% patients with MM resulting from a complex interaction of factors including energy intake, degree of motor impairment, and hydrocephalus [48, 49]. Nutritional counseling and mobility programs should be initiated early to prevent the development of obesity.
- Tethered cord syndrome occurs in 10–30% patients with MM. Common orthopedic findings include gait changes, loss of muscle strength, spasticity, progressive scoliosis, back pain, and leg pain. The orthopedic team must be actively vigilant for any signs of tethered cord during every examination of a patient with MM. An MMT should be performed at least annually to screen for any unexpected changes over time.

References

1. Racial/ethnic differences in the birth prevalence of spina bifida—United States, 1995–2005. MMWR Morb Mortal Wkly Rep. 2009;57(53):1409–13.
2. McLone DG, Bowman RM. Overview of the management of myelomeningocele (spina bifida). In: Armsby C, editor. UpToDate. Waltham, MA: UpToDate; 2018.
3. Bowman RM, McLone DG, Grant JA, Tomita T, Ito JA. Spina bifida outcome: a 25-year prospective. Pediatr Neurosurg. 2001;34(3):114–20.
4. Piatt JH Jr. Treatment of myelomeningocele: a review of outcomes and continuing neurosurgical considerations among adults. J Neurosurg Pediatr. 2010;6(6):515–25.
5. Dias L. Myelomeningocele and intraspinal lipoma. In: Sponseller P, editor. Orthopaedic knowledge update: pediatrics. 2nd ed. Rosemont, IL: American Academy of Orthopaedic Surgeons; 2002. p. 249–59.
6. Meuli M, Meuli-Simmen C, Hutchins GM, Seller MJ, Harrison MR, Adzick NS. The spinal cord lesion in human fetuses with myelomeningocele: implications for fetal surgery. J Pediatr Surg. 1997;32(3):448–52.
7. Walsh DS, Adzick NS, Sutton LN, Johnson MP. The Rationale for in utero repair of myelomeningocele. Fetal Diagn Ther. 2001;16(5):312–22.
8. Heuer GG, Moldenhauer JS, Scott AN. Prenatal surgery for myelomeningocele: review of the literature and future directions. Childs Nerv Syst. 2017;33(7):1149–55.
9. Prevention of neural tube defects: results of the Medical Research Council Vitamin Study. MRC Vitamin Study Research Group. Lancet. 1991;338(8760):131–7.
10. Czeizel AE, Dudas I. Prevention of the first occurrence of neural-tube defects by periconceptional vitamin supplementation. N Engl J Med. 1992;327(26):1832–5.
11. Recommendations for the use of folic acid to reduce the number of cases of spina bifida and other neural tube defects. MMWR Morb Mortal Wkly Rep. 1992;41(Rr-14):1–7.
12. Padmanabhan R. Etiology, pathogenesis and prevention of neural tube defects. Congenit Anom (Kyoto). 2006;46(2):55–67.

13. Luo J, Balkin N, Stewart JF, Sarwark JF, Charrow J, Nye JS. Neural tube defects and the 13q deletion syndrome: evidence for a critical region in 13q33-34. Am J Med Genet. 2000;91(3):227–30. https://doi.org/10.1002/(sici)1096-8628(20000320)91:3<227::aid-ajmg14>3.0.co;2-i.
14. McDonald CM, Jaffe KM, Mosca VS, Shurtleff DB. Ambulatory outcome of children with myelomeningocele: effect of lower-extremity muscle strength. Dev Med Child Neurol. 1991;33(6):482–90.
15. Seitzberg A, Lind M, Biering-Sorensen F. Ambulation in adults with myelomeningocele. Is it possible to predict the level of ambulation in early life? Childs Nerv Syst. 2008;24(2):231–7.
16. Sharrard WJ. The orthopaedic surgery of spina bifida. Clin Orthop Relat Res. 1973;92:195–213.
17. Swank M, Dias LS. Walking ability in spina bifida patients: a model for predicting future ambulatory status based on sitting balance and motor level. J Pediatr Orthop. 1994;14(6):715–8.
18. Mazur JM, Shurtleff D, Menelaus M, Colliver J. Orthopaedic management of high-level spina bifida. Early walking compared with early use of a wheelchair. J Bone Joint Surg Am. 1989;71(1):56–61.
19. Stillwell A, Menelaus MB. Walking ability in mature patients with spina bifida. J Pediatr Orthop. 1983;3(2):184–90.
20. Swaroop VT, Dias L. Orthopedic management of spina bifida. Part I: hip, knee, and rotational deformities. J Child Orthop. 2009;3(6):441–9.
21. Swaroop VT, Dias L. Orthopaedic management of spina bifida-part II: foot and ankle deformities. J Child Orthop. 2011;5(6):403–14.
22. Asher M, Olson J. Factors affecting the ambulatory status of patients with spina bifida cystica. J Bone Joint Surg Am. 1983;65(3):350–6.
23. Selber P, Dias L. Sacral-level myelomeningocele: long-term outcome in adults. J Pediatr Orthop. 1998;18(4):423–7.
24. Adzick NS, Thom EA, Spong CY, Brock JW 3rd, Burrows PK, Johnson MP, et al. A randomized trial of prenatal versus postnatal repair of myelomeningocele. N Engl J Med. 2011;364(11):993–1004.
25. Moldenhauer JS, Soni S, Rintoul NE, Spinner SS, Khalek N, Martinez-Poyer J, et al. Fetal myelomeningocele repair: the post-MOMS experience at the Children's Hospital of Philadelphia. Fetal Diagn Ther. 2015;37(3):235–40.
26. Danzer E, Gerdes M, Bebbington MW, Sutton LN, Melchionni J, Adzick NS, et al. Lower extremity neuromotor function and short-term ambulatory potential following in utero myelomeningocele surgery. Fetal Diagn Ther. 2009;25(1):47–53.
27. Danzer E, Thomas NH, Thomas A, Friedman KB, Gerdes M, Koh J, et al. Long-term neurofunctional outcome, executive functioning, and behavioral adaptive skills following fetal myelomeningocele surgery. Am J Obstet Gynecol. 2016;214(2):269e1–8.
28. Farmer DL, Thom EA, Brock JW 3rd, Burrows PK, Johnson MP, Howell LJ, et al. The management of myelomeningocele study: full cohort 30-month pediatric outcomes. Am J Obstet Gynecol. 2018;218(2):256e1–e13.
29. Gabrieli AP, Vankoski SJ, Dias LS, Milani C, Lourenco A, Filho JL, et al. Gait analysis in low lumbar myelomeningocele patients with unilateral hip dislocation or subluxation. J Pediatr Orthop. 2003;23(3):330–4.
30. Swaroop VT, Dias LS. What is the optimal treatment for hip and spine in myelomeningocele? In: Wright JG, editor. Evidence-based orthopaedics. Amsterdam, the Netherlands: Elsevier Health Sciences; 2008. p. 273–7.
31. Akbar M, Bresch B, Seyler TM, Wenz W, Bruckner T, Abel R, et al. Management of orthopaedic sequelae of congenital spinal disorders. J Bone Joint Surg Am. 2009;91(Suppl 6):87–100.
32. Guille JT, Sarwark JF, Sherk HH, Kumar SJ. Congenital and developmental deformities of the spine in children with myelomeningocele. J Am Acad Orthop Surg. 2006;14(5):294–302.
33. Sarwark JF (Ed.). Caring for the Child with Spina Bifida: Shriners Hospitals for Children, Symposium, Oak Brook, Illinois, April 14–16, 2000. AAOS Symposia Series, Shriners Hospitals for Children; 657 pgs.

34. Arkin C, Ihnow S, Dias L, Swaroop VT. Midterm results of the ponseti method for treatment of clubfoot in patients with spina bifida. J Pediatr Orthop. 2018;38(10):e588–92. https://doi.org/10.1097/BPO.0000000000001248.
35. de Carvalho NJ, Dias LS, Gabrieli AP. Congenital talipes equinovarus in spina bifida: treatment and results. J Pediatr Orthop. 1996;16(6):782–5.
36. Gunay H, Sozbilen MC, Gurbuz Y, Altinisik M, Buyukata B. Incidence and type of foot deformities in patients with spina bifida according to level of lesion. Childs Nerv Syst. 2016;32(2):315–9.
37. Westcott MA, Dynes MC, Remer EM, Donaldson JS, Dias LS. Congenital and acquired orthopedic abnormalities in patients with myelomeningocele. Radiographics. 1992;12(6):1155–73.
38. Gerlach DJ, Gurnett CA, Limpaphayom N, Alaee F, Zhang Z, Porter K, et al. Early results of the Ponseti method for the treatment of clubfoot associated with myelomeningocele. J Bone Joint Surg Am. 2009;91(6):1350–9.
39. Janicki JA, Narayanan UG, Harvey B, Roy A, Ramseier LE, Wright JG. Treatment of neuromuscular and syndrome-associated (nonidiopathic) clubfeet using the Ponseti method. J Pediatr Orthop. 2009;29(4):393–7.
40. Matar HE, Beirne P, Garg NK. Effectiveness of the Ponseti method for treating clubfoot associated with myelomeningocele: 3-9 years follow-up. J Pediatr Orthop B. 2017;26(2):133–6.
41. Dobbs MB, Purcell DB, Nunley R, Morcuende JA. Early results of a new method of treatment for idiopathic congenital vertical talus. Surgical technique. J Bone Joint Surg Am. 2007;89(Suppl 2 Pt.1):111–21.
42. Chalayon O, Adams A, Dobbs MB. Minimally invasive approach for the treatment of nonisolated congenital vertical talus. J Bone Joint Surg Am. 2012;94(11):e73.
43. Chan Y, Selvaratnam V, Garg N. A comparison of the Dobbs method for correction of idiopathic and teratological congenital vertical talus. J Child Orthop. 2016;10(2):93–9.
44. Yang JS, Dobbs MB. Treatment of congenital vertical talus: comparison of minimally invasive and extensive soft-tissue release procedures at minimum five-year follow-up. J Bone Joint Surg Am. 2015;97(16):1354–65.
45. Sarwark JF, Weber DT, Gabrieli AP, McLone DG, Dias L. Tethered cord syndrome in low motor level children with myelomeningocele. Pediatr Neurosurg. 1996;25(6):295–301.
46. Akbar M, Bresch B, Raiss P, Furstenberg CH, Bruckner T, Seyler T, et al. Fractures in myelomeningocele. J Orthop Traumatol. 2010;11(3):175–82.
47. Haas RE, Kecskemethy HH, Lopiccolo MA, Hossain J, Dy RT, Bachrach SJ. Lower extremity bone mineral density in children with congenital spinal dysfunction. Dev Med Child Neurol. 2012;54(12):1133–7.
48. Fiore P, Picco P, Castagnola E, Palmieri A, Levato L, Gremmo M, et al. Nutritional survey of children and adolescents with myelomeningocele (MMC): overweight associated with reduced energy intake. Eur J Pediatr Surg. 1998;8(Suppl 1):34–6.
49. Mita K, Akataki K, Itoh K, Ono Y, Ishida N, Oki T. Assessment of obesity of children with spina bifida. Dev Med Child Neurol. 1993;35(4):305–11.

Chapter 34
Spinal Muscular Atrophy

Jill E. Larson

Epidemiology and Pathophysiology

Spinal muscular atrophy (SMA) is a neuromuscular disorder characterized by degeneration of the cell body within an alpha motor neuron located in the anterior horn of the spinal cord, leading to a lower motor neuron-type syndrome. This degeneration occurs due to insufficient production of survival motor neuron (SMN) protein, induced by mutations or deletions in *SMN1* gene (exon 7 and/or 8) on chromosome 5q, inherited in an autosomal recessive manner. The extent of clinical involvement depends on the number of copies of the SMN2 "rescue" gene, which produces mostly nonfunctional SMN protein ($\leq$2 copies = more severe disease; 3–4 copies = milder disease) [1].

The resulting clinical phenotype and musculoskeletal manifestations stem from associated progressive muscle atrophy, weakness, and paralysis [1–3]. SMA phenotypes are classified based on the age of onset and maximum motor function achieved: Type I patients are very weak infants unable to sit unsupported; Type II patients are non-ambulatory children who can sit independently; Type III patients ambulate as children, but may lose functional gait in adulthood, whereas Type IV remain ambulatory as adults [1].

The incidence of SMA is approximately 1 in 11,000 live births [3]. Of those, approximately 58% have SMA type I, 29% have SMA Type II, and 13% have SMA Type III. SMA type IV is rarely observed [4]. Using a life table analysis of the rate of birth prevalence and estimated survival for each type of SMA, the prevalence of symptomatic SMA cases in the United States in 2016 was 9429 [5].

J. E. Larson (✉)
Ann & Robert H. Lurie Children's Hospital, Chicago, IL, USA
e-mail: jlarson@luriechildrens.org

J. F. Sarwark, R. L. Carl (eds.), *Orthopaedics for the Newborn and Young Child*,
https://doi.org/10.1007/978-3-031-11136-5_34

From a musculoskeletal and orthopedic perspective, hip instability is common in SMA patients, and the incidence corresponds to SMA type with increased frequency in the non-ambulatory population. Hip subluxation occurs in approximately 30–40% of SMA type II patients and 10–30% of SMA type III patients. Hip dislocation occurs in approximately 30% of SMA type II patients and 20–30% of SMA type III patients [6, 7].

Many SMA patients demonstrate concomitant hip and spine deformity (Fig. 34.1). A radiographic study of 49 SMA patients revealed that 26 patients (53%) had both hip and spine pathology. Of those patients, 58% had concurrent spine and hip abnormalities; 38% developed a spinal deformity prior to hip instability, and 4% developed hip instability prior to spinal deformity [8]. Thus, orthopedic surgeons must evaluate the entire axial skeleton and consider how surgical interventions will impact overall sitting and standing posture, position and function of the hip, pelvis, and spine.

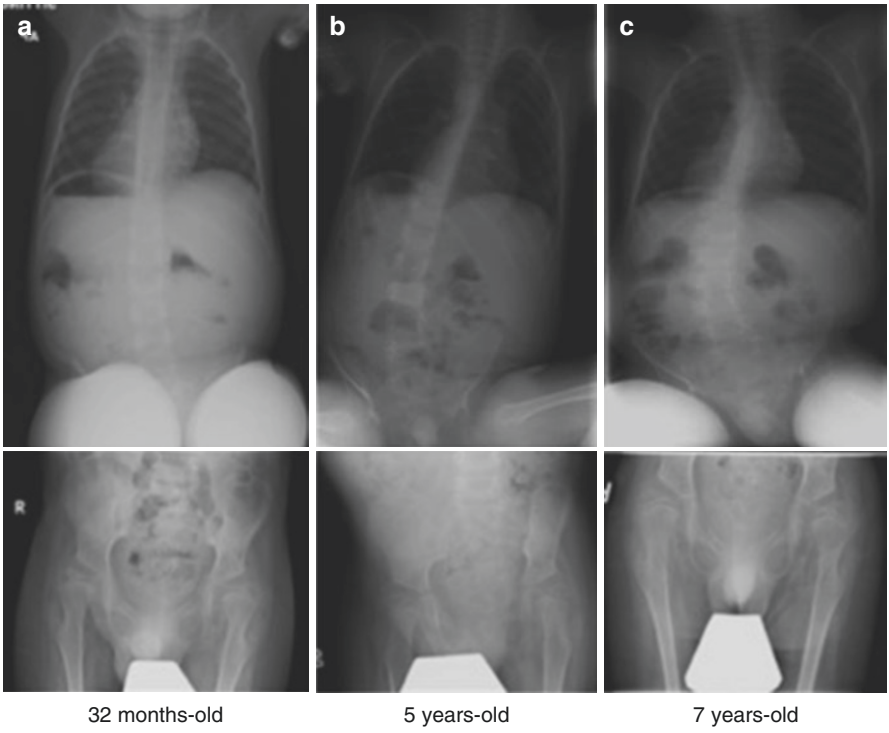


Fig. 34.1 Associated hip and spine pathology in SMA: (**a**) Bilateral symmetric coxa valgus with 50% migration index, mild acetabular dysplasia, level pelvis, no scoliosis; (**b**) Progressive, symmetric posterolateral hip subluxation, mild acetabular dysplasia, level pelvis, no scoliosis; (**c–f**) Neuromuscular scoliosis contributes to associated pelvic obliquity and "windswept posture" (adducted right hip, abducted left hip); failure to control pelvic obliquity with initial spinal instrumentation contributes to vertical migration of the right hemipelvis, relative acetabular dysplasia with uncovering of right hip progressing to near dislocation of right hip

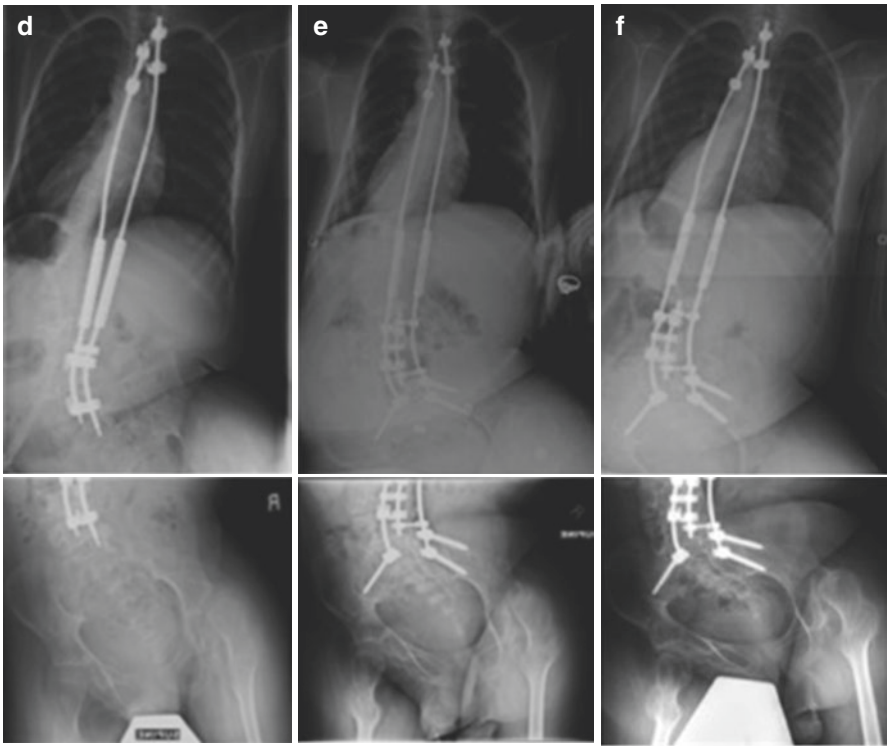


Fig. 34.1 (continued)

Clinical Presentation: History and Physical

The clinical findings of SMA include progressive, symmetric, proximal greater than distal muscle weakness affecting the legs more than the arms, sparing the facial muscles, but involving bulbar muscles. Tongue fasciculation and absent muscle stretch reflexes are hallmark features of Types I and II. Sensation and cognition are typically preserved for all types. Semi-annual examinations should be performed to assess strength, joint range of motion, motor function, and gait (where appropriate) [9–13]. The primary orthopedic surgical issues involve the axial skeleton (i.e., pelvis and spine).

Besides affecting the musculoskeletal system, these patients suffer from respiratory, nutritional, and metabolic dysfunction that contribute to morbidity and mortality. In Types I and II, weakness of the intercostal muscles, with relative sparing of the diaphragm, is associated with the development of a "bell-shaped" thorax that influences pulmonary function and the need for supplemental respiratory support [14]. Therefore, these patients require comprehensive care involving the participation of multiple disciplines to manage their medical comorbidities, especially during the perioperative phase. Patients should be evaluated on a regular basis by

pulmonologists, neurologists, gastroenterologists, feeding specialists, physiatrists, and orthopedists. Pulmonary function testing is essential to assess fitness for surgery when indicated.

As these patients are mostly non-ambulatory, they are susceptible to osteopenia and insufficiency fractures depending on disease severity and weight-bearing capacity. As such, an evaluation of their "bone health" should also be performed regularly. This evaluation typically includes 25OH vitamin D levels and DEXA scanning; this is particularly helpful for preoperative assessment of bone quality and for cases where internal fixation devices may be used.

Radiographic Studies/Testing/Evaluation

A formal radiographic surveillance program to monitor hip instability or spinal deformity in SMA has not been established in the literature. However, if a patient is greater than 6 months of age upon initial evaluation, an AP pelvis should be obtained to document baseline hip status. Subsequent radiographs should be obtained if there is any concerning change in examination, such as decreased hip range of motion, increasing contractures or positive Galeazzi, Ortolani, and/or Barlow findings. This orthopedic evaluation should occur routinely at 6 month intervals with XRs of the pelvis obtained yearly [15]. Similarly, if the clinical exam is concerning increasing spinal curvature or asymmetric sitting balance, a sitting PA and lateral spine XR should be obtained. A patient reporting new hip, back, or thigh pain should prompt further radiographic evaluation of the hip and spine.

An AP and lateral Pelvis is typically obtained in the supine position in young or non-ambulatory patients. If there is a concern for hip instability in an ambulatory patient, then a standing AP pelvis should be obtained to document the hip position with weight-bearing forces.

DEXA scans should be obtained on all SMA patients to assess for osteopenia and guide medical management. DEXA scans should also be routinely evaluated preoperatively to assess bone quality and to help guide surgeons on instrumentation choices in the setting of poor bone quality.

Finally, surgical planning for hip reconstruction should include a CT scan of the pelvis to assess for acetabular dysplasia and identify the areas of poor femoral head coverage to guide surgical decision-making on the need for any type of pelvic osteotomy.

Treatment/Management

Traditionally, the treatment of SMA has been supportive, focusing on maximizing pulmonary and musculoskeletal function with the use of bracing and therapy services. Recently however the US FDA approved Nusinersen, the first

disease-modifying drug treatment for SMA. Nusinersen is an antisense oligonucleotide drug that modifies pre-messenger RNA splicing of the SMN2 gene thereby promoting increased production of a biologically effective, full-length SMN protein [16]. It is administered to the cerebrospinal fluid via intrathecal injection to deliver the drug directly to the spinal motor neurons which degenerate in patients with SMA [17]. Predicated on the positive results of two phase 3, randomized placebo-controlled studies, Nusinersen was officially released for the treatment of all forms of SMA in December 2016 [18, 19].

While long-term follow-up studies of the impact of Nusinersen are pending, initial results of infants treated with intrathecal Nusinersen have improved motor function and increased survival without the permanent use of assisted ventilation compared to those undergoing a sham procedure (ENDEAR study) [16]. These infants continue to be followed in an open-label extension study (SHINE) [20], to assess the effects of longer treatment duration on motor function and quality of life. The results of a clinical trial investigating the use of Nusinersen for older SMA type II and III children (2–12 years of age at enrollment) also demonstrate clinically significant improvement in motor function compared to controls (CHERISH trial) [21]. Nusinersen and other drugs in the development pipeline have the potential to change the natural history of SMA, its clinical symptoms and management approach. However, even with the introduction of disease-modifying treatments, a multidisciplinary approach is paramount to comprehensive management.

Use of Physical Therapy and Orthoses

Physical therapy alone has not been demonstrated to maintain hip stability or to prevent hip instability. Use of hip abduction splints to concentrically relocate an unstable hip may help prevent hip adduction contractures and maintain functional range of motion for toileting, hygiene, and activities of daily living, but will not prevent progressive hip instability, especially if there is associated pelvic obliquity and scoliosis.

The objectives for musculoskeletal management in SMA type II sitters are to restore or promote function and mobility by preventing joint contractures and scoliosis. Modalities for stretching include techniques that can be achieved manually with orthoses, splints, active-assistive stretching, and serial casting to maintain functional range of motion about the shoulder, elbow, wrist, hip, knee, and ankles in SMA type II patients. Fujak and colleagues recommended the utilization of a self-propelled or power-assisted wheelchair in non-ambulatory children as early as age 3 to facilitate functional independence [22]. Additionally, a walking apparatus (e.g., swivel walker or gait trainer) or passive support for standing (e.g., standing frame) should be initiated as early as age 2 for patients with appropriate head and trunk control, or with the support of a soft thoracolumbar orthosis for those lacking sufficient trunk control. Aquatic-based therapies are useful for strengthening of core and hip girdle musculature and simulated walking.

In patients with SMA type III, musculoskeletal management should focus on improving core, hip girdle, and quadriceps muscle strength, balance, and functional mobility. Both closed and open chain strengthening using dynamic and static forms should be incorporated into an exercise program to maintain functional ambulation. Many SMA patients become overweight and obese after reaching puberty, making it difficult for already weak muscles to support the trunk during walking. For example, the gluteus medius must generate nearly 3× body weight to support the trunk during single-legged stance, so that for every pound in body mass over ideal body weight, means that the gluteus medius must generate an additional 3 pounds of force.

Nonoperative Management of Scoliosis

As sitting balance and pelvic obliquity can significantly impact the stability of a hip in a non-ambulatory SMA patient, any associated spinal curvature needs to be addressed. While bracing in neuromuscular scoliosis has not been shown to slow curve progression, bracing with a thoracolumbar-sacral orthoses (TLSO) may be used to augment truncal support in patients unable to sit or stand independently. Bracing is particularly critical for SMA type I and type II patients to promote postural stabilization and maximize function. There is no consensus on the type of brace to be used, but a circumferential, anterior opening, soft spinal thoracolumbar orthosis with a large anterior window to allow for abdominal expansion and to facilitate diaphragmatic breathing is typically recommended [18]. Cervical bracing can be used for head support for safety and transportation. Thoracic bracing is not typically used during walking in SMA type III, as it may adversely affect ambulatory ability.

Operative Management of Hip Instability

With Nusinersen treatment changing the prognosis of SMA, hip reconstructive surgery should be considered as an SMA patient's ambulatory status may improve, and the surgical complication rate is similar to reconstructive hip surgery in other neuromuscular conditions such as Cerebral Palsy [23, 24].

The consensus opinion of orthopedic surgeons participating in a recent European Neuromuscular Centre (ENMC) International Workshop suggested that unilateral and bilateral hip instability should be surgically managed in patients with significant pain or impaired function [18]. Consideration should be given to the radiographic appearance of the hip including the migration index or percent coverage of the femoral head by the acetabulum and the depth of the acetabulum indicated by the acetabular index when contemplating surgical intervention (Fig. 34.2).

Concerning surgery of the hip in SMA, there is little controversy for children who can or may walk: reconstruct the hip if it is unstable (i.e., subluxated or

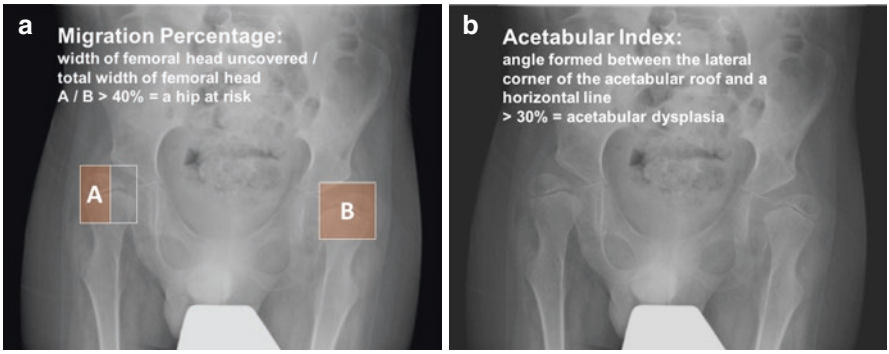


Fig. 34.2 Radiographic monitoring of the hip in SMA with (**a**) Migration percentage and (**b**) Acetabular index

dislocated). For non-ambulatory children undergoing Nusinersen therapy, surgical intervention may be indicated for the maintenance of pelvic alignment, to treat or prevent the onset of painful arthritis, to address pelvic obliquity associated with scoliosis, and to improve sitting balance. Surgical reconstruction of coxa valga with an associated dysplastic acetabulum is less complicated in children less than 10 years of age when the triradiate cartilage is open. However, Nusinersen is not curative and therefore persistent muscle weakness and asymmetry can still lead to recurrent coxa valga and hip subluxation in younger patients (<6 years of age), requiring revision surgery at a later stage. In the young adult patient with a chronically dislocated hip, leave the hip dislocated if painless. However, if the patient has pain related to coxa arthrosis, then a salvage procedure may be indicated, such as a McHale procedure (femoral head resection arthroplasty plus Shanz proximal femoral valgus osteotomy) [25].

Before addressing the osseous component of hip instability, orthopedic surgeons must be aware of associated joint contractures that often need to be surgically released to facilitate range of motion and upright posture in stander/gait trainer. Contractures of lower extremities develop early and increase progressively with age in non-ambulatory patients with SMA. Typically, contractures involve muscles crossing two joints including (1) the hamstrings (causing knee flexion contractures), (2) the psoas, adductor longus, and gracilis (contributing to flexion and adduction contractures), and (3) the gastrocnemius (causing ankle equinus) [22]. Joint contractures with functional limitations affecting gait are less common in SMA type III but should be monitored nonetheless [26]. Judicious fractional lengthening of musculotendinous contractures should be considered to improve functional joint range of motion and to improve sitting/standing posture, recognizing that lengthening a weak muscle weakens it further. Especially for the hip, there should be at least 45° of abduction to perform a proximal varus derotational osteotomy (VDRO), so often an open adductor tenotomy/myotomy is required prior to the VDRO.

A proximal varus derotational osteotomy (VDRO) (Fig. 34.3) is often combined with acetabuloplasty if there is significant posterior/lateral subluxation of the

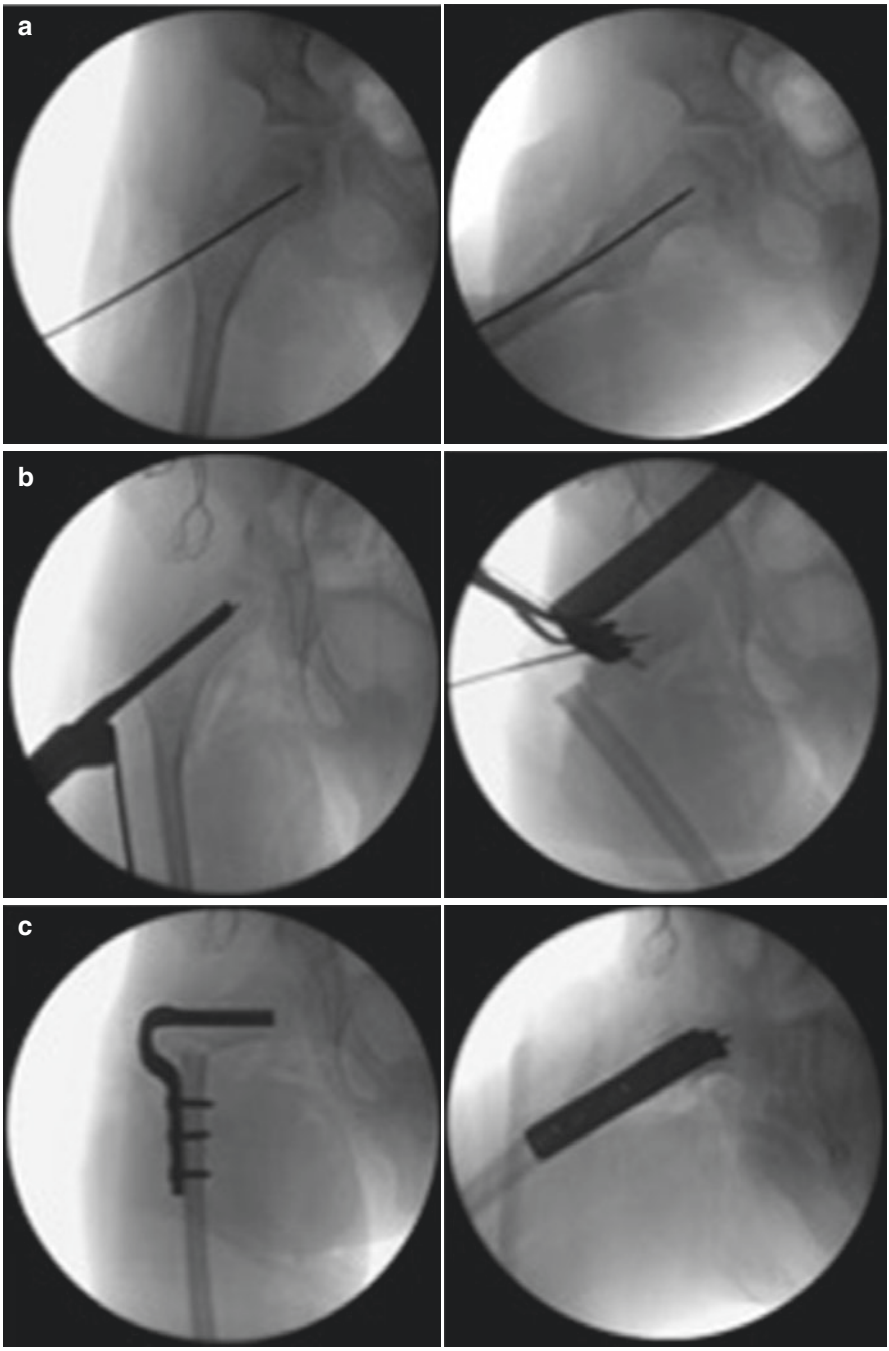


Fig. 34.3 Surgical procedure Varus Derotation Osteotomy: (**a**) Initial placement of guidewires for a 90° fixed angle blade plate; (**b**) chisel and derotational k-wire placement prior to subtrochanteric osteotomy with improved varus alignment of the femoral head; (**c**) final instrumentation with blade plate noting medialization of the femoral shaft and improved but still deficient femoral head coverage suggesting need for acetabuloplasty

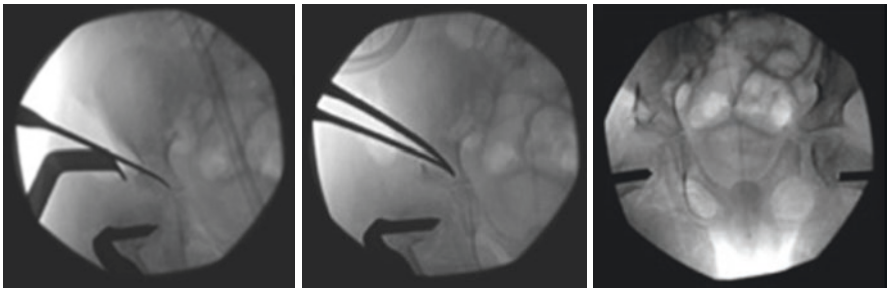


Fig. 34.4 Surgical procedure peri-acetabular osteotomies: open triradiate cartilage-Pemberton-Degas-San Diego type reshaping acetabuloplasty with hinging through the triradiate cartilage and autograft

femoral head with associated dysplasia of the acetabulum (Fig. 34.4). A preoperative CT scan of the pelvis is useful for surgical planning of the acetabuloplasty, although not universally indicated. An intraoperative hip arthrogram can also help facilitate the decision-making process on whether or not to perform an acetabuloplasty, noting that a large cartilaginous anlage outlined by the arthrogram may not require acetabuloplasty given the remodeling potential of the hip joint in young children. Occasionally, an open hip reduction is required for severely dislocated hips that do not reduce.

Operative Management of Scoliosis

The treatment of scoliosis in patients with SMA is complicated because a limited time frame exists in which these patients have a sufficient lung capacity to successfully undergo spinal surgery. If spinal surgery is not performed within this narrow window, the opportunity to maximize medical management is lost and patients are less likely to survive spinal surgery [27]. The goal of surgical intervention is to maximize physical function and pulmonary function. While pulmonary function in SMA types II and III continue to decline after scoliosis surgery, the rate of decline is less marked and prolonged survival of patients justifies the aggressive management of scoliosis to prevent deformity progression and improve sitting comfort [28, 29].

Surgical intervention (Fig. 34.5) should be considered according to curve magnitude (i.e., major curve Cobb angle $\geq 50°$) and rate of progression ($\geq 10°$ per year) [18]. Other factors, such as decreasing respiratory function, parasol rib deformity, hyperkyphosis, and adverse effects on functional mobility, pelvic obliquity, and trunk imbalance should also be considered. Mesfin and colleagues proposed a surgical algorithm for selecting spinal construct type and levels [30]: (1) growing rod anchored to pelvis with skeletal age ≤ 9 years and curve magnitude $>70°$, and (2) posterior spinal fusion with pedicle screws at most levels T2 to pelvis for patients with open triradiate cartilage and curve magnitude $>70°$, skeletal age > 10 years.

Recent literature has supported the use of growing rod constructs in the treatment of scoliosis in the skeletally immature SMA patient population [31, 32]. McElroy

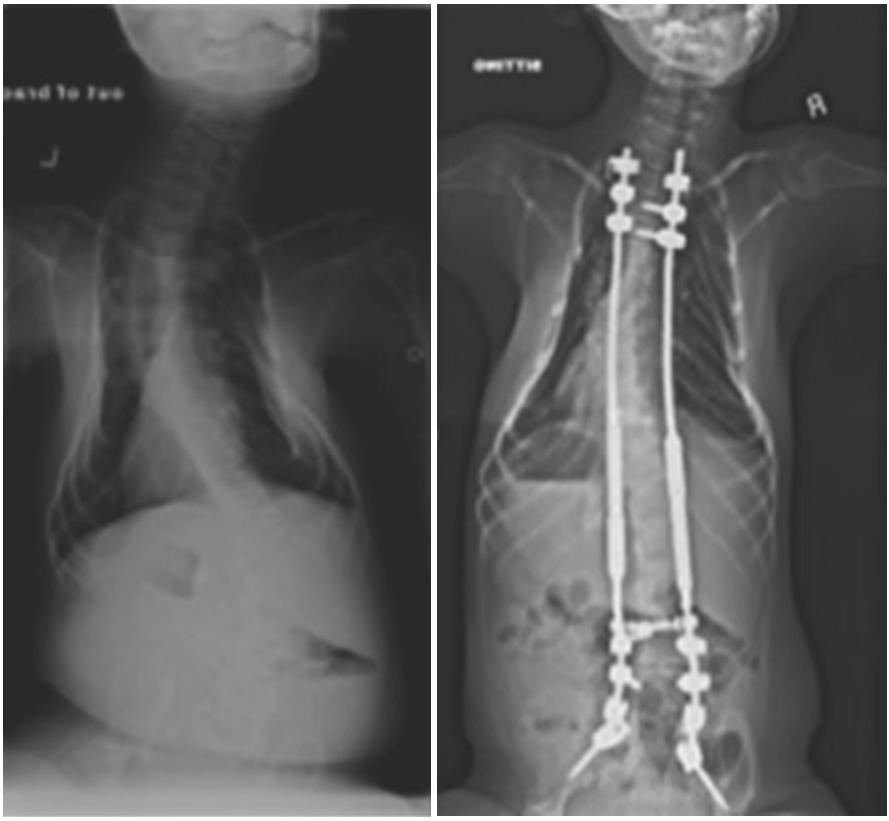


Fig. 34.5 Surgical indication for spinal instrumentation in SMA: 9-year-old male with SMA type II with preoperative right thoracolumbar curve of 58° underwent growing rod instrumentation with improved pelvic obliquity and spinal alignment

and colleagues retrospectively reviewed 15 patients with SMA with an average of 54-month follow-up and compared them to 80 growing rod patients with early onset idiopathic scoliosis. They found an improvement in trunk height (average increase of 8.7 ± 3.2 cm) and space available for lung ratio (increased from 0.86 ± 0.15 to 0.94 ± 0.21) in the SMA cohort while also controlling curve magnitude (Cobb angle decreased from 89 ± 19° to 55 ± 17°) and pelvic obliquity. Although they noted a longer hospital stay in the SMA cohort, there was a lower complication rate than the age-matched growing rod patients with idiopathic scoliosis [31].

Clinical Pearls

- The incidence of hip instability in SMA type II and III ranges from 30 to 40% with an increased risk of dislocation in the non-ambulatory patient population.

- SMA patients should be evaluated for decreased hip motion, associated contractures, and signs of hip instability every 6 months with radiographic AP and lateral XRs obtained on an annual basis.
- While nonoperative management of hip instability has traditionally been supportive in the literature, Nusinersen is changing the trajectory of functionality and ambulation in SMA patients. Thus, hip reconstructive surgery should be considered in a clinically or radiographically unstable hip as the surgical complication rate is similar to reconstructive hip surgery in other neuromuscular conditions.
- More than 50% of SMA patients demonstrate concomitant hip and spine deformity; therefore, a clinician must evaluate the entire axial skeleton and consider how surgical interventions will impact the overall sitting/standing posture, position, and function of the hip, pelvis, and spine.

References

1. Lunn MR. Wang ch Spinal muscular atrophy. Lancet. 2008;371(9630):2120–33.
2. Lefebvre S, Bürglen L, Reboullet S, Clermont O, Burlet P, Viollet L, et al. Identification and characterization of a spinal muscular atrophy-determining gene. Cell. 1995;80(1):155–65.
3. Sugarman EA, Nagan N, Zhu H, Akmaev VR, Zhou Z, Rohlfs EM, et al. Pan-ethnic carrier screening and prenatal diagnosis for spinal muscular atrophy: clinical laboratory analysis of >72,400 specimens. Eur J Hum Genet. 2012;20(1):27–32.
4. Ogino S, Wilson RB. Spinal muscular atrophy: molecular genetics and diagnostics. Expert Rev Mol Diagn. 2004;4(1):15–29.
5. Lally C, Jones C, Farwell W, Reyna SP, Cook SF, Flanders WD. Indirect estimation of the prevalence of spinal muscular atrophy Type I, II, and III in the United States. Orphanet J Rare Dis. 2017;12(1):175.
6. Sporer SM, Smith BG. Hip dislocation in patients with spinal muscular atrophy. J Pediatr Orthop. 2003;23(1):10–4.
7. Zenios M, Sampath J, Cole C, Khan T, Galasko CS. Operative treatment for hip subluxation in spinal muscular atrophy. J Bone Joint Surg Br. 2005;87(11):1541–4.
8. Patel J, Shapiro F. Simultaneous progression patterns of scoliosis, pelvic obliquity, and hip subluxation/dislocation in non-ambulatory neuromuscular patients: an approach to deformity documentation. J Child Orthop. 2015;9(5):345–56.
9. Glanzman AM, Mazzone E, Main M, Pelliccioni M, Wood J, Swoboda KJ, et al. The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND): test development and reliability. Neuromuscul Disord. 2010;20(3):155–61.
10. Mazzone E, Bianco F, Main M, van den Hauwe M, Ash M, de Vries R, et al. Six minute walk test in type III spinal muscular atrophy: a 12month longitudinal study. Neuromuscul Disord. 2013;23(8):624–8.
11. Mazzone E, Bianco F, Martinelli D, Glanzman AM, Messina S, De Sanctis R, et al. Assessing upper limb function in nonambulant SMA patients: development of a new module. Neuromuscul Disord. 2011;21(6):406–12.
12. Vuillerot C, Payan C, Iwaz J, Ecochard R, Bérard C, MFM Spinal Muscular Atrophy Study Group. Responsiveness of the motor function measure in patients with spinal muscular atrophy. Arch Phys Med Rehabil. 2013;94(8):1555–61.
13. Montes J, McDermott MP, Martens WB, Dunaway S, Glanzman AM, Riley S, et al. Six-Minute Walk Test demonstrates motor fatigue in spinal muscular atrophy. Neurology. 2010;74(10):833–8.

14. Livingston K, Zurakowski D, Snyder B, Growing Spine Study Group; Children's Spine Study Group. Parasol rib deformity in hypotonic neuromuscular scoliosis: a new radiographic definition, and a comparison of short-term treatment outcomes with VEPTR and growing rods. Spine (Phila Pa 1976). 2015;40(13):E780–6.
15. Prior TW, Finanger E. Spinal muscular atrophy. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, LJH B, Stephens K, Amemiya A, editors. GeneReviews®. Seattle, WA: University of Washington, Seattle; 2000.
16. Finkel RS, Mercuri E, Darras BT, Connolly AM, Kuntz NL, Kirschner J, et al. Nusinersen versus sham control in infantile-onset spinal muscular atrophy. N Engl J Med. 2017;377(18):1723–32.
17. Evers MM, Toonen LJ, van Roon-Mom WM. Antisense oligonucleotides in therapy for neurodegenerative disorders. Adv Drug Deliv Rev. 2015;87:90–103.
18. Finkel RS, Sejersen T, Mercuri E, ENMC SMA Workshop Study Group. 218th ENMC international workshop: revisiting the consensus on standards of care in SMA Naarden, The Netherlands, 19-21 February 2016. Neuromuscul Disord. 2017;27(6):596–605.
19. Mendell JR, Al-Zaidy S, Shell R, Arnold WD, Rodino-Klapac LR, Prior TW, et al. Single-dose gene-replacement therapy for spinal muscular atrophy. N Engl J Med. 2017;377(18):1713–22.
20. A study for participants with spinal muscular atrophy (SMA) who previously participated in nusinersen (ISIS 396443) investigational studies. (SHINE). Identification No.NCT02594124. https://clinicaltrials.gov/ct2/show/NCT02594124.
21. Mercuri E, Darras BT, Chiriboga CA, Day JW, Campbell C, Connolly AM, et al. Nusinersen versus sham control in later-onset spinal muscular atrophy. N Engl J Med. 2018;378:625–35.
22. Fujak A, Kopschina C, Gras F, Forst R, Forst J. Contractures of the lower extremities in spinal muscular atrophy type II. Descriptive clinical study with retrospective data collection. Ortop Traumatol Rehabil. 2011;13(1):27–36.
23. Larson J, Snyder J, Troy M, Whitaker AT, Snyder B. Short-term clinical outcomes of hip reconstructive surgery in patients with spinal muscular atrophy. Unpublished manuscript; 2018.
24. Ruzbarsky JJ, Beck NA, Baldwin KD, Sankar WN, Flynn JM, Spiegel DA. Risk factors and complications in hip reconstruction for nonambulatory patients with cerebral palsy. J Child Orthop. 2013;7(6):487–500.
25. McHale KA, Bagg M, Nason SS. Treatment of the chronically dislocated hip in adolescents with cerebral palsy with femoral head resection and subtrochanteric valgus osteotomy. J Pediatr Orthop. 1990;10(4):504–9.
26. Wang HY, Ju YH, Chen SM, Lo SK, Jong YJ. Joint range of motion limitations in children and young adults with spinal muscular atrophy. Arch Phys Med Rehabil. 2004;85(10):1689–93.
27. Robinson D, Galasko CS, Delaney C, Williamson JB, Barrie JL. Scoliosis and lung function in spinal muscular atrophy. Eur Spine J. 1995;4(5):268–73.
28. Phillips DP, Roye DP Jr, Farcy JP, Leet A, Shelton YA. Surgical treatment of scoliosis in a spinal muscular atrophy population. Spine (Phila Pa 1976). 1990;15(9):942–5.
29. Chng SY, Wong YQ, Hui JH, Wong HK, Ong HT, Goh DY. Pulmonary function and scoliosis in children with spinal muscular atrophy types II and III. J Paediatr Child Health. 2003;39(9):673–6.
30. Mesfin A, Sponseller PD, Leet AI. Spinal muscular atrophy: manifestations and management. J Am Acad Orthop Surg. 2012;20(6):393–401.
31. McElroy MJ, Shaner AC, Crawford TO, Thompson GH, Kadakia RV, Akbarnia BA, et al. Growing rods for scoliosis in spinal muscular atrophy: structural effects, complications, and hospital stays. Spine (Phila Pa 1976). 2011;36(16):1305–11.
32. Chandran S, McCarthy J, Noonan K, Mann D, Nemeth B, Guiliani T. Early treatment of scoliosis with growing rods in children with severe spinal muscular atrophy: a preliminary report. J Pediatr Orthop. 2011;31(4):450–4.

Chapter 35
Duchenne Muscular Dystrophy

Angielyn San Juan and John J. Grayhack

Brief Overview of the Condition

Duchenne muscular dystrophy is the most common form of muscular dystrophy, characterized by progressive, symmetrical proximal muscle group weakness of the lower extremities, with subsequent involvement of the shoulder girdle. The progressive nature of the disease results in loss of ambulatory ability, soft tissue contractures, and progressive spinal deformity. It is an X-linked recessive disorder; therefore, almost exclusively affects males. The disease results from a complete absence of dystrophin protein, a molecule essential for the function of muscle cells. A milder form of the disease, Becker muscular dystrophy, is a result of a qualitative reduction in dystrophin protein. While serum lab tests may be indicative of the diagnosis, genetic testing is definitive. The overall goals of treatment in Duchenne and Becker muscular dystrophy are maintenance of the functional capacity of the child which is achieved through medical therapies, use of orthoses, surgical management of musculoskeletal deformity, cardiopulmonary management, and genetic counseling.

A. S. Juan
Department of Orthopaedics, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA

Northshore University Health System, Skokie, IL, USA
e-mail: asanjuan@northshore.org

J. J. Grayhack (✉)
Baylor College of Medicine, Houston, TX, USA
e-mail: jgrayhack@luriechildrens.org

J. F. Sarwark, R. L. Carl (eds.), *Orthopaedics for the Newborn and Young Child*,
https://doi.org/10.1007/978-3-031-11136-5_35

Background: Epidemiology and Pathophysiology

Duchenne muscular dystrophy is an X-linked, recessive disorder, affecting 1 in 3500 males. It occurs as a result of a mutation encoding the dystrophin gene on the short arm of the X chromosome (Xp21.2) [1]. A significant majority (60%) of these mutations are due to large insertions or deletions of the gene, while other mutations are secondary to point mutations or frameshift rearrangements. Patients with Duchenne muscular dystrophy have a complete absence of the dystrophin gene and subsequent protein. Similarly, Becker muscular dystrophy is an X-linked, recessive disorder affecting 1 in 30,000 males, resulting from a reduction in quantity or alteration in size of the dystrophin protein, and consequently less significant clinical manifestations.

Dystrophin is a structural protein that links the internal cytoskeleton to the extracellular matrix. The dystrophin-associated protein complex binds to the intracellular surface of the sarcolemma and attaches to the plasma membrane of myofibers, acting to stabilize the fibers during muscle contraction. Dystrophin protein is present in skeletal, smooth, and cardiac muscles. Absence of dystrophin, as with Duchenne muscular dystrophy, leads to loss of the dystrophin protein complex, instability of the sarcolemma and myofibers, and results in necrosis of the muscle fiber [1]. These areas of necrosis undergo an inflammatory process, followed by progressive fibrosis and replacement of the muscle with fibroadipose tissue. Due to dystrophin's role in smooth, skeletal, and cardiac muscle, this progressive injury is manifested in both the musculoskeletal and cardiac systems. Forms of the protein have also been found in the brain, and contribute to neuronal instability [2]. The degeneration of specific muscle groups occurs initially at the proximal muscles of the hip girdle then those of the shoulder, leading to weakness of the lower and upper extremities, subsequent fibroadipose replacement of muscle tissue and eventual contractures of the joints.

Clinical Presentation: History and Physical

The clinical manifestations of Duchenne muscular dystrophy become apparent between 3 and 6 years of age. Families may report delay or failure to achieve independent ambulation, difficulty in reciprocal walking or running, inability to hop, skip or run, toe walking, frequent tripping or falling, or challenges participating in sports or play in recess and gym [3].

The presentation of symptoms occurs in a gradual manner. Patients will first have weakness involving the muscles around the hip. The weakness particularly affects the gluteus maximus, gluteus medius, quadriceps, and tibialis anterior muscles; and it does so in a symmetric, progressive pattern. The abdominal musculature are then affected, followed by the shoulder girdle muscles. Pseudohypertrophy of the calves that is frequently characteristic of this disease is secondary to fatty infiltration [4]. Because this necrosis and fibroadipose infiltration also affect cardiac musculature, initial cardiac manifestations include sinus tachycardia with progression to heart failure secondary to cardiomyopathy. Patients with Duchenne muscular dystrophy also have neurocognitive issues, performing at 1 standard deviation below the

general population on full-scale IQ measurements. Though the amount of intellectual disability is variable, individuals with Duchenne or Becker muscular dystrophy have higher frequencies of cognitive disability when compared to their non-affected peers. Often, the cognitive and behavioral diagnoses are delayed, as the focus on management is typically on medical treatment and intervention [5].

The pattern of gait abnormality progresses in a predictable fashion. At first, the child's cadence may appear slowed, but, as the weakness of the lower extremities progresses, the child's gait pattern changes to compensate for weak muscle groups. Sutherland identified three features that quantified disease progression; decreased gait cadence, increased anterior pelvic tilt, and decreased dorsiflexion angle during swing phase. The decreased gait cadence occurs due to the gradual weakening of the lower extremities. As hip extension becomes more difficult, in order to shift the center gravity posteriorly and maintain standing posture and balance, increasing lumbar lordosis becomes more prominent. The child then progresses to having a wide-based, waddling gait with swaying of the trunk to compensate for weak hip abduction (gluteus medius) [6]. Ankle dorsiflexion is progressively affected and leads to fixed ankle plantar flexion; evidenced by toe walking, walking cadence, and poor balance. Foot inversion and varus are the last to develop due to weak peroneal and tibialis posterior muscles, respectively. Weakness of the shoulder girdle follows 3–5 years after the presentation of lower extremity symptoms.

Clinical diagnosis can be inferred from physical examination. The clinical manifestations of Duchenne's muscular dystrophy include the Gower sign (Fig. 35.1), indicative of lower extremity weakness and the Meyeron sign, indicative of upper extremity weakness [7]. The patient manifesting Gowers sign is unable to rise from

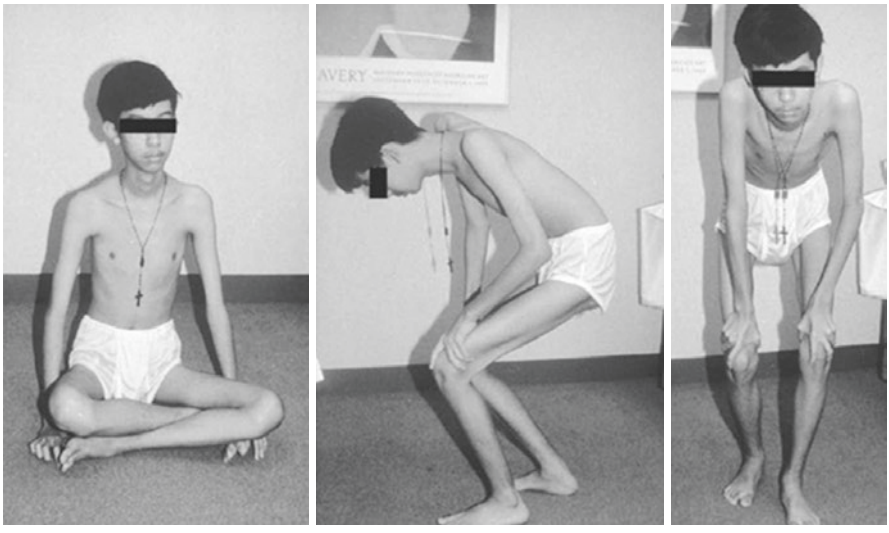


Fig. 35.1 Clinical manifestations of Duchenne's muscular dystrophy. Reprinted with permission from Wolters Kluwer Health/Lippincott Williams & Wilkins. Thompson GH, Berenson FR. Chapter 16 Other Neuromuscular Disorders. In Lovell WW, Weinstein SL, Flynn JM (Eds.). Lovell and Winter's Pediatric Orthopaedics, 7th ed. Philadelphia, PA: Wolters Kluwer Health, Inc./Lippincott Williams and Wilkins, 2013 [8]

the floor using hip and knee extension and therefore "walks" his hands across the floor and upward along the legs to achieve a standing position. Meyerson documented the increasing difficulty in lifting a child beneath their arms as their shoulder girdle musculature became weaker. The child will slip through one's grasp. Hip abduction contractures often result as the disease progresses, in addition to tendo-Achilles contractures.

Loss of ambulatory ability occurs at approximately ages 10–12 years. The eventual loss of ankle dorsiflexors in combination with the weak hip extensors and abductors causes the child to have significantly slowed gait and difficulty with balance in upright stance. After becoming full-time wheelchair ambulators, many of these patients will develop progressive spinal deformity, often displaying the pattern of kyphoscoliosis.

Fatal complications include both cardiac and pulmonary compromise. Cardiomyopathy occurs due to fatty infiltration of normal myocardium, leading to progressive heart failure, worsening cardiomyopathy, and possible conduction abnormalities. Loss of respiratory muscle strength leads to diminished ventilation and ineffective cough, resulting in pneumonia, atelectasis, and respiratory insufficiency [9].

Evaluation

In the setting of signs and symptoms suggesting the diagnosis, further diagnostic evaluation should be initiated. Serum creatinine phosphate kinase (CPK) levels are elevated 200–300 times the normal value, although as the disease progresses, profound muscle loss and necrosis lead to lower values of CPK. Further, confirmatory testing includes genetic testing and less commonly open muscle biopsy [5].

Management

Management of children with Duchenne and Becker muscular dystrophy should be approached in a multidisciplinary fashion with the overall goals of preserving ambulatory ability and prolonging life expectancy through managing pulmonary, cardiac, and musculoskeletal progression of the disease process. The team of specialists involved includes neurology, orthopedics, physical medicine and rehabilitation, pulmonology, cardiology, physical and occupational therapist, orthoptist, nutritional evaluation and support, and psychology [5, 10]. Medical and surgical interventions are dictated by the child's stage of disease: presymptomatic, early and late ambulatory, and early and late non-ambulatory.

Medical therapies to maintain and improve strength have been utilized to preserve ambulation. Glucocorticoids are the only medication currently available that has been shown to slow the decline in muscle strength and function in Duchenne muscular dystrophy, in addition to reducing the risk of progression of scoliosis.

Initial randomized control trials of patients treated with glucocorticoids for 6 months showed improvements in muscle strength, with the dose of 0.75 mg/kg daily [11]. Further studies investigating higher doses showed no clinical benefit. Both prednisone and deflazacort have been utilized, though deflazacort appears to have similar clinical results with diminished side effects such as weight gain [12].

Steroids should not be initiated in the child who is still gaining motor skills, especially those children under the age of 2 years of age [5]. The decision for initiation of steroid therapy depends upon many factors, including functional ability, ambulatory status, and onset of motor impairment or decline. Once steroid treatment is begun, the patient should be monitored for side effects including obesity, growth retardation, bone demineralization and fracture risk, immune/adrenal suppression, hypertension, glucose intolerance, and peptic ulcer disease.

Physical therapy is important to preserve the function of affected muscle groups, maximize and accommodate for alterations in gait, passive stretching to prevent the development of contractures, serial assessment of muscle strength, and input for alterations in equipment (walker, wheelchair, etc.) [13]. Patients can be instructed on home exercises targeting weak muscle groups and to continue stretching of involved joints to further prevent the development of contractures [14].

Orthoses help the ambulatory child maintain functional gait, stance, and limb alignment with the use of molded ankle-foot-orthoses (AFOs). Orthoses help both in the early stages of the disease in contracture prevention, as well as in later stages after surgical correction. Patients who are wheelchair-bound and forgo spinal surgical intervention may utilize spinal orthoses for truncal support, alignment, and comfort but there is no evidence of impact on curve progression with bracing [15].

Due to the medical therapy with chronic steroids and diminished ambulation/weight bearing, children with Duchenne and Becker muscular dystrophy have decreased bone mineral density resulting in increased fracture risk. Lower extremity fractures in muscular dystrophy patients who are still ambulatory at an increased risk for resulting in permanent loss of ambulatory ability during fracture healing [16, 17]. Therefore, fracture management focused on early mobilization and weight bearing. This may include open reduction internal fixation of fractures to help facilitate early mobility [14].

Surgical management of contractures is considered to be prolonged ambulation, targeting hip flexion and abduction contractures, knee flexion contractures, along with equinus and equinovarus foot contractures [18]. Percutaneous techniques may be utilized to achieve contracture releases. The use of orthoses postoperatively is critically important to maintain the corrected position of the affected joints, as well as to assist in an earlier return to ambulation [19].

Unless treated with early, chronic steroids, the majority of patients with Duchenne muscular dystrophy (95%) progressively develop scoliosis (Fig. 35.2). This typically occurs at the decline of ambulation, and is rapidly progressive. Surgical correction of scoliosis not only improves sitting posture and balance but can aid in maintaining cardiopulmonary function [20]. With knowledge of the natural history of both the progress of scoliosis and the patient's declining pulmonary function, spinal fusion with instrumentation may be considered for patients with curves greater than 20° [21].

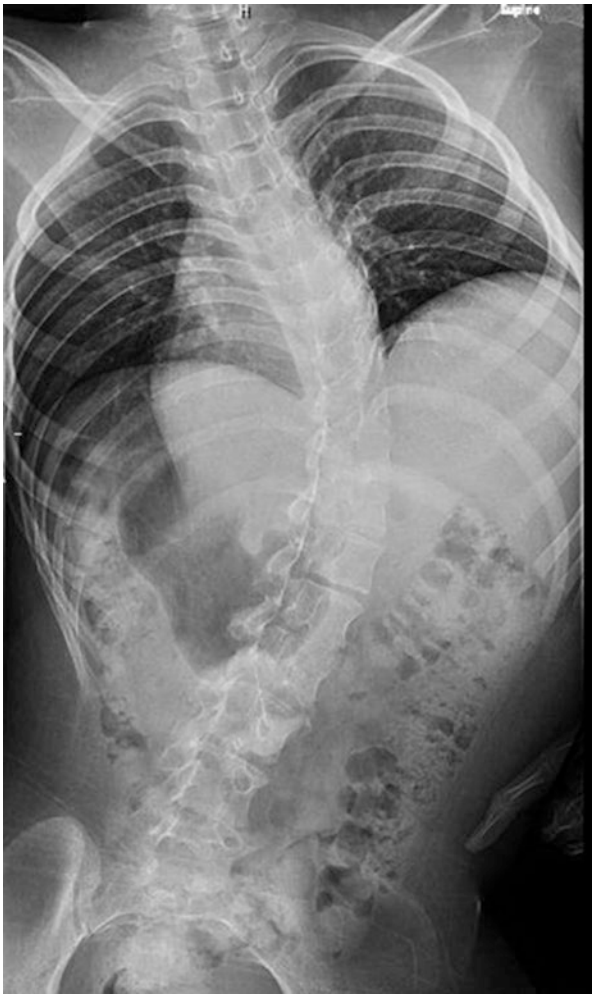


Fig. 35.2 Radiograph demonstrating scoliosis

Clinical Vignettes/Clinical Pearls

- Duchenne muscular dystrophy is a progressive, symmetrical proximal muscle group weakness of the lower extremities and the shoulder girdle.
- The inheritance is X-linked, recessive therefore exclusively affects males.
- Patients have the loss of ambulatory ability and orthopedic manifestations include soft tissue contractures and progressive spinal deformity.
- Medical therapy with the administration of glucocorticoids helps preserve and improve muscle strength and delay or avoid certain associated complications.

References

1. Nowak KJ, Davies KE. Duchenne muscular dystrophy and dystrophin: pathogenesis and opportunities for treatment. EMBO Rep. 2004;5(9):872–6. https://doi.org/10.1038/sj.embor.7400221.
2. Aartsma-Rus A, GInjaar IB, Bushby K. The importance of genetic diagnosis for Duchenne muscular dystrophy. J Med Genet. 2016;(53):145–51. https://doi.org/10.1136/jmedgenet-2015-103387&domain=pdf&date_stamp=2016-01-11.
3. Orrell RW. Diagnosing and managing muscular dystrophy. Practitioner. 2012;1754:21–4.
4. Omonova U. Clinical-diagnostic features of duchenne muscular dystrophy in children. Int J Biomed. 2013;4:266–8.
5. Bushby K, Birnkrant DJ, Clemens PR, Cripe L, Kaul A, Kinnett K, et al. Review diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and pharmacological and psychosocial management. Lancet. 2009;9(1):1–17. https://doi.org/10.1016/S1474-4422(09)70271-6.
6. Goudriaan M, Van den Hauwe M, Dekeerle J, Verhelst L, Molenaers G, Goemans N, DesloovereK. Gait deviations in Duchenne muscular dystrophy—Part 1. A systematic review. Gait Posture. 2018 May;62(247–261) https://doi.org/10.1016/j.gaitpost.2018.03.020.
7. Iyadurai SJP, Kissel JT. The limb-girdle muscular dystrophies and the dystrophinopathies. Continuum (Minneap Minn). 2016;22(6):1954–77. https://doi.org/10.1212/CON.0000000000000406.
8. Thompson GH, Berenson FR. Chapter 16: Other neuromuscular disorders. In: Lovell WW, Weinstein SL, Flynn JM, editors. Lovell and winter's pediatric orthopaedics. 7th ed. Philadelphia, PA: Wolters Kluwer Health, Inc./Lippincott Williams and Wilkins; 2013.
9. Ryder S, Leadley RM, Armstrong N, Westwood M, de Kock S, Butt T, et al. The burden, epidemiology, costs and treatment for Duchenne muscular dystrophy: an evidence review. Orphanet J Rare Dis. 2017;12(79). https://doi.org/10.1186/s13023-017-0631-3.
10. Apkon SD, Alman B, Birnkrant DJ, Fitch R, Lark R, Mackenzie W, et al. Orthopedic and surgical management of the patient with Duchenne muscular dystrophy. Pediatrics. 2018;142(Suppl 2):S82–9. https://doi.org/10.1542/peds.2018-0333J.
11. Falzarano MS, Scotton C, Passarelli C, Ferlini A. Duchenne muscular dystrophy: from diagnosis to therapy. Molecules. 2015;20(10):18168–84. https://doi.org/10.3390/molecules201018168.
12. Lebel DE, Corston JA, McAdam LC, Biggar WD, Alman BA. Glucocorticoid treatment for the prevention of scoliosis in children with Duchenne muscular dystrophy: long-term follow-up. J Bone Joint Surg Am. 2013;95(12):1057–61. https://doi.org/10.2106/JBJS.L.01577.
13. Vignos PJ, Wagner MB, Kaplan JS, Spencer GE. Predicting the success of reambulation in patients with Duchenne muscular dystrophy. J Bone Joint Surg. 1983;65(6):1–10.
14. Bushby K, Finkel R, Birnkrant DJ, Case LE, Clemens PR, Cripe L, et al. Review diagnosis and management of Duchenne muscular dystrophy, part 2: implementation of multidisciplinary care. Lancet Neurol. 2010;9(2):177–89. https://doi.org/10.1016/S1474-4422(09)70272-8.
15. Garg S. Management of scoliosis in patients with Duchenne muscular dystrophy and spinal muscular atrophy: a literature review. J Pediatr Rehabil Med. 2016;9(1):23–9. https://doi.org/10.3233/PRM-160358.
16. Bell JM, Shields MD, Watters J, Hamilton A, Beringer T, Elliott M, et al. Interventions to prevent and treat corticosteroid-induced osteoporosis and prevent osteoporotic fractures in Duchenne muscular dystrophy. Cochrane Database Syst Rev. 2017;28(Suppl 1):CD010899. https://doi.org/10.1002/14651858.CD010899.pub2.
17. King WM, Ruttencutter R, Nagaraja HN, Matkovic V, Landoll J, Hoyle C, et al. Orthopedic outcomes of long-term daily corticosteroid treatment in Duchenne muscular dystrophy. Neurology. 2007;68:1607–13.
18. Leitch KK, Raza N, Biggar D, Stephen D, Wright JG, Alman B. should foot surgery be performed for children with Duchenne muscular dystrophy? J Pediatr Orthop. 2004;25(1):95–7.

19. Smith SE, Green NE, Cole RJ, Robinson JD, Fenichel GM. Prolongation of ambulation in children with Duchenne muscular dystrophy by subcutaneous lower limb tenotomy. J Pediatr Orthop. 1993;13(3):336–40.
20. Archer JE, Gardner AC, Roper HP, Chikermane AA, Tatman AJ. Duchenne muscular dystrophy: the management of scoliosis. J Spine Surg. 2016;2(3):185–94. https://doi.org/10.21037/jss.2016.08.05.
21. Shapiro F, Zurakowski D, Bui T, Darras BT. Progression of spinal deformity in wheelchair-dependent patients with Duchenne muscular dystrophy who are not treated with steroids. Bone Joint J. 2014;496(1):100–5. https://doi.org/10.1302/0301-620X.96B1.

Chapter 36
Myotonic Dystrophy

Mary E. Dubon, Elizabeth N. Martin, and Andrea Paulson

Background

The myotonic disorders encompass a range of genetic conditions unified by the presence of myotonia, a failure of muscle relaxation after activation [1]. They include the dystrophic myotonias: myotonic dystrophy (DM1) (or Steinart disease) and proximal myotonic myopathy (PROMM) (also known as myotonic muscular dystrophy 2 (DM2)), and the non-dystrophic myotonias: myotonia congenita, paramyotonia congenita, potassium aggravated myotonia, potassium-sensitive periodic paralysis, and chondrodystrophic myotonia (or Schwartz-Jampel Syndrome). There is significant variation in presentation, diagnosis, and management across these heterogeneous conditions [2–6]. In this chapter, we will focus on myotonic dystrophy type 1 (DM1).

M. E. Dubon (✉)
Department of Pediatric Rehabilitation, Spaulding Rehabilitation Hospital, Charlestown, MA, USA

Department of Orthopedics and Division of Sports Medicine, Boston Children's Hospital, Boston, MA, USA

Department of Physical Medicine and Rehabilitation, Harvard Medical School, Boston, MA, USA
e-mail: mary.dubon@childrens.harvard.edu

E. N. Martin
Department of Pediatric Rehabilitation Medicine, Mary Bridge Children's Hospital, Tacoma, WA, USA
e-mail: martieli2012@alumni.ohsu.edu

A. Paulson
Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, OH, USA
e-mail: andrea.paulson@Cchmc.org

J. F. Sarwark, R. L. Carl (eds.), *Orthopaedics for the Newborn and Young Child*,
https://doi.org/10.1007/978-3-031-11136-5_36

Epidemiology/Pathophysiology of DM1

DM1 is an autosomal dominant muscular dystrophy affecting both skeletal muscle and smooth muscle, as well as ocular structures, the myocardium, the central nervous system (CNS), the endocrine system, and the gastrointestinal system. It was first described by Steinert and colleagues in 1909, and, therefore, has also been called Steinert's disease.

DM1 is the most common inherited neuromuscular disorder of adults, with a prevalence reported between 1 per 7500 or 8000, and is due to mutation of the myotonin protein kinase (DMPK) gene at 19q13.3 [2–6]. The genetic mutation, discovered in 1992, results in expansion of an unstable CTG trinucleotide repeat in the three untranslated regions of the gene [6]. Higher numbers of trinucleotide repeats often correspond with greater clinical severity [7–9]. Unaffected individuals typically have <34 repeats of this trinucleotide, with a repeat length greater than 34 considered abnormal [2]. Individuals with mild DM1 may have 50–150, while those with classic DM1 usually have between 100 and 1000 repeats, and those with congenital DM1 typically have well over 1000 repeats [7]. The DMPK gene encodes myosin kinase in skeletal muscle; however, systemic symptoms including involvement of the CNS, endocrine, gastrointestinal, cardiac, and ocular systems have all been well described. mRNA splicing abnormalities have been proposed as mechanisms underlying these systemic features [6].

Age of presentation also correlates with severity of presentation in DM1 [7]. The concept of "anticipation" is well described, in which offspring of individuals with DM1 may have expansion of the trinucleotide repeat with increased severity of presentation. Variation in clinical presentation can also be seen due to variable penetrance, somatic mosaicism, maternal expansion bias, or aberrant pre-mRNA splicing [2, 10].

Common Clinical Presentation

Corresponding with the underlying genetics, clinical findings fall within a continuum from mild to severe, classified as mild, classic, and congenital phenotypes. Other classification systems exist, including by age of onset, such as that used by the French DM-scope registry, which describes congenital form (mild to severe symptoms detected in the first month of birth), infantile form (onset between 1 month and 10 years), juvenile form (onset between 10 and 20 years), adult form (onset between 20 and 40 years), or late-onset form (onset after 40 years of age) [9]. Congenital DM1 is considered a distinct form from severe classical DM1, with very distinct clinical features.

Individuals with mild or late-onset DM1 are expected to have a normal life span, with symptoms including development of cataracts and mild myotonia. Myotonia is

usually described as difficulty releasing objects or painful muscle cramping, and again may be seen in both mild and classic DM1 [1]. There may be no clear family history, often leading to missed diagnosis, but extended family history should be explored given the inheritance pattern. Referral for ophthalmologic evaluation is important, and findings of early and characteristic posterior subcapsular cataracts may actually lead to diagnosis [6].

Adults with classic DM1 may initially present with muscle weakness in the face, mouth, neck, hands, or distal legs [2, 3, 5, 6]. This group commonly presents with the classic "myotonic facies," including temporal wasting, ptosis, and tented upper lip due to facial weakness [3]. Individuals with classic DM1 may have a shortened life span and may have more functional impairments related to muscle weakness, myotonia, cataracts, and cardiac conduction abnormalities [2]. Weakness may involve the neck flexors as well as distal hands and feet, leading to difficulty with fine motor tasks or foot drop [2, 5]. One study suggests that 95% of patients remain ambulatory after a mean disease duration of 16–19 years due to the slow progression of the condition [3, 11]. Myotonia may affect grip as well as chewing, speaking, or swallowing if there is bulbar involvement [12]. An ophthalmologic evaluation may confirm the presence of cataracts. Cardiac evaluation may reveal arrhythmias or conduction abnormalities, and rarely dilated cardiomyopathy [2, 5, 6, 8, 13]. Insulin resistance is frequently seen, and endocrine abnormalities may also include low endogenous testosterone and testicular atrophy [6]. Gastrointestinal symptoms of irritable bowel syndrome may be present [6]. Sleep apnea and excessive daytime sleepiness may interfere with employment or school [14]. Childhood-onset DM1 shares many features with classic adult-onset DM1, but with increased severity and earlier presentation. Greater facial weakness and intellectual disability also distinguish this category [15].

Infants with congenital DM1 are distinct from the classic and childhood-onset forms of DM1, and may initially present in utero with polyhydramnios and decreased fetal movements [6]. At delivery, characteristic features include hypotonia, generalized weakness, and respiratory insufficiency, with a high risk of fatality due to respiratory failure [3, 6]. Cerebral atrophy and ventricular enlargement have been described [3]. Infants with congenital DM1 classically continue to be distinguished by marked hypotonia and may have facial or generalized weakness, respiratory difficulties, intellectual disability, and musculoskeletal findings such as congenital talipes equinovarus (clubfoot) [5, 6]. Myotonia is usually absent in infancy [3]. Severe facial weakness may result in an inverted V-shaped upper lip [2, 5, 6]. Motor and cognitive milestones are typically delayed; however, with survival into childhood, children have some improvements in motor milestones, and most will walk independently. Learning differences are present, and school supports are critical. Early cardiac abnormalities are also seen and early referral to cardiology is important [8]. As these children reach adulthood, they may begin to develop features of "classic" DM1 with gradually worsening weakness and they may go on to develop cardiorespiratory failure in their 20s–40s [6, 8, 9].

General Medical Evaluation and Treatment

Neurologic

Clinical presentation of weakness, myotonia, hypotonia, characteristic cataracts, cardiac abnormalities, or family history may all lead to a question of DM1. Diagnostic evaluation includes clinical history and exam for characteristic features. Historically, electromyography was a key component of diagnosis, demonstrating myotonia with a repetitive, spontaneous discharge of muscle fibers that waxes and wanes in amplitude and frequency [1]. Electromyography may still be helpful in cases where clinical findings may be more subtle, but with a clearly defined genetic mutation, genetic testing is now standard for diagnosis. Muscle biopsy demonstrates a greater concentration of central nuclei, varied fiber diameter, and increased fibrosis and adipose deposition [6]. These findings are also present in DM2, but DM1 is distinguished by predominantly type 1 fiber atrophy as opposed to type 2 [6]. In DM1, nuclear clumps are present in end stage muscle [6].

Cognitive delays vary with severity of disease and CTG expansion size but are common in this group. One study, among children ages 7–24, described a prevalence of learning disability in 95% of children with severe congenital disease, 83% of children with mild congenital disease, and 89% of children with childhood DM1 [16]. A second demonstrated a mean IQ of 73.6 in patients ages 7–24 with DM1, a mean verbal IQ of 80.2, and performance IQ of 72.95 [17]. Cognitive testing in this group identified severe deficits in visual attention and visual-spatial construction abilities. There is still conflicting evidence on increased rates of autism correlating with DM1. Clinicians should consider the need for school supports in these children if not already provided, including evaluation for an individualized education plan (IEP), and possible referral for neuropsychological testing to identify areas of needed support [18].

Cardiac

Cardiac evaluation is important, specifically looking for myocardium changes causing ventricular arrhythmias or atrioventricular (AV) block that can lead to sudden death in DM1 [19–22]. Cardiac involvement may include conduction defects, ventricular dysfunction, as well as supraventricular or ventricular arrhythmias [23]. Higher numbers of trinucleotide repeats with greater clinical severity have been shown to directly correspond with higher incidence of cardiac arrhythmia, with one study identifying only 17% of individuals with >1000 repeats having normal ECGs [8]. Close monitoring with a cardiologist and consideration of pacing intervention may improve outcomes.

Respiratory

Dysfunction of the respiratory system is a known component of the systemic involvement in DM1. A leading cause of death in DM1 is cardiorespiratory complications [6, 19–21]. Noninvasive ventilation has improved survival [24]. Among adults with DM1, one study showed the mean baseline vital capacity to be <50% of normal, with further decline related to age, body mass index, and CTG expansion size [25]. Decline in both inspiratory and expiratory muscle strength was noted, but the weakness was predominantly in expiratory muscles. Consideration of Pulmonology referral for respiratory screening and consideration of aids such as cough assist devices can assist in prevention of potentially life-threatening complications.

Fatigue and slowness are also common concerns in DM1, with one study demonstrating sleep abnormalities in 66% of children with childhood-onset DM1 [14]. Consideration of disordered sleep and intervention from sleep medicine may improve school performance for children with DM1.

Ophthalmology

Findings may include cataracts, as well as abnormalities in oculomotor and stereopsis warranting ophthalmologic evaluation [26].

Endocrinology

As mentioned above, endocrinologic disorders including diabetes, hypogonadism, or adrenal sufficiency may be more prevalent in this population and warrant Endocrinology evaluation and monitoring, particularly in older teens and adults [27].

Rehabilitation

Deficits in fine motor and gross motor skills, as well as fatigue and pain with chewing, may be seen related to myotonia. Rehabilitation medicine can work with patients to identify adaptive strategies to improve participation and endurance in school and in the community, and to help reduce discomfort.

Table 36.1 reviews the commonly associated comorbidities and their management strategies [1, 6, 8, 14, 16–54]. Given the complexity of the condition and the

Table 36.1 Systematic manifestations of DM1 [1, 6, 8, 14, 16–54]

Organ system	Details of possible comorbidities	Initial primary care evaluation	Management
Neurologic	Cognitive impairment/ intellectual disability – Mild to moderate intellectual disability – Global developmental delay in some cases – Difficulties with alertness, attention, planning ahead, decision-making, visual processing, and spatial processing are common	– History components suggesting cognitive or developmental difficulties – Brief cognitive screen in clinic – Screen for daytime sleepiness and/or sleep disorders that may affect cognitive performance	– Early Intervention Services – Individualized Education Plan (IEP) – Neuropsychology referral for testing can help elucidate strengths and areas of concern – Daytime sleepiness or sleep disorders should be evaluated and managed by a Sleep Specialist
	Hypotonia is common and leads to delays in gross motor milestones including rolling, sitting, and walking Distal muscle weakness	– History assessment evaluating attainment of milestones – Examination of muscle tone, strength, and developmental skills	– Referral to early intervention services, which includes therapy to work on gross motor, fine motor, and cognitive skills
	Myotonia or the inability for a muscle to relax is common but is not always present at a young age	– History evaluating for myotonia or muscle cramping – Physical examination evaluating for grip myotonia or percussion myotonia	– Referral to Neurology for evaluation and management
HEENT	Congenital cataracts	– History components suggesting visual difficulties – Eye exam looking for red reflex	– Referral to Ophthalmology for prompt evaluation and treatment
	Low visual acuity and/or astigmatism	– History components suggesting visual difficulties – Visual screening examination	– Referral to Ophthalmology for evaluation and treatment
	Ptosis and facial muscle weakness	– History components pointing to mention of ptosis or facial weakness – Cranial nerve exam evaluating for ptosis	– Referral for speech therapy may be warranted if facial weakness affects speech or swallow

Table 36.1 (continued)

Organ system	Details of possible comorbidities	Initial primary care evaluation	Management
Cardiovascular	Several Cardiovascular comorbidities have been described: Atrial fibrillation Atrioventricular (AV) block Conduction defects Supraventricular arrhythmias Ventricular arrhythmias Ventricular dysfunction There is a risk of sudden death due to cardiovascular comorbidities Later in the disease process, cardiomyopathy can present and lead to heart failure	– History and physical examination screening for cardiac concerns – Screening ECG	– Evaluation and management by Cardiology is recommended for individuals with DM1 given the high incidence of cardiac concerns in this population
Respiratory	Hypotonia can result in respiratory concerns and need to be monitored The most common cause of death in DM1 is cardiorespiratory complications	– History and physical examination focused on respiratory concerns	– Referral to Pulmonology is critical for this population for evaluation and treatment of respiratory comorbidities
Gastrointestinal	Feeding difficulties are common and secondary to muscle weakness in the jaw and mouth making sucking and swallowing difficult Constipation is common as well as gallbladder dysfunction, abdominal pain, diarrhea, pseudo-obstruction, gastroparesis, and failure to thrive	– History and physical examination screening for feeding or gastrointestinal concerns	– Referral for speech therapy for feeding difficulties – Surgical referral for gastrostomy tube in cases where this is necessary for adequate nutrition – Gastroenterology referral for gastrointestinal concerns of gallbladder dysfunction, abdominal pain, diarrhea, pseudo-obstruction, or gastroparesis

(continued)

Table 36.1 (continued)

Organ system	Details of possible comorbidities	Initial primary care evaluation	Management
Endocrine	Insulin resistance if present can lead to hyperglycemia or diabetes	– History and physical examination evaluating for concerns of insulin resistance – Screening bloodwork for insulin resistance	– Hyperglycemia treatment, which may include referral to Endocrinology for specialty care
	Motor impairments: – Upper extremity fine motor difficulty – Lower extremity gross motor difficulty, including delays in walking		
Musculoskeletal	Neurogenic scoliosis or kyphoscoliosis	– History and physical examination evaluation for scoliosis from a young age – Radiographs of the spine	– Orthopedic referral for ongoing evaluation and management of scoliosis
	Foot conditions – Congenital talipes equinovarus – Equinus – Equinovarus – Planovalgus	– History and physical examination with special attention to foot conditions – Congenital talipes equinovarus may be detected with prenatal ultrasound	– Referral to Orthopedics for evaluation and management
	Contractures of the upper and lower extremities – Distal>proximal	– History of physical examination revealing decreased range of motion at joints	– Daily stretching – Referral to Rehabilitation Medicine for consideration of therapy or bracing—in some cases, this may lead to a surgical referral
	Lower extremity torsion deformities – Femoral anteversion – Internal tibial torsion – External tibial torsion	– History of in-toeing or out-toeing – Physical examination including evaluation of gait	– Orthopedic referral for evaluation. In most situations, torsion deformities do not require surgical intervention, but in some cases, surgery is recommended.

Table 36.1 (continued)

Organ system	Details of possible comorbidities	Initial primary care evaluation	Management
General considerations	Anesthesia complications can occur	– History of prior anesthesia or respiratory complications – General physical examination, including cardiac and respiratory examinations	– Anesthesiologist should be made aware of DM1 diagnosis for any patient who will be undergoing anesthesia for surgery or other procedures

multiple organ system involvement, interdisciplinary care is important to provide the best care for these patients. This includes the involvement of specialists in the disciplines of Neurology, Rehabilitation Medicine, Cardiology, Pulmonary, Orthopedics, Ophthalmology, and, at times, Gastroenterology. Many institutions host interdisciplinary clinics for children with neuromuscular conditions, so patients can see providers from multiple specialties on the same day.

Orthopedic Considerations

Motor Impairments

As described above, the classic pattern of muscle involvement in myotonic dystrophy includes facial weakness and distal upper and lower extremity weakness [39]. Due to this, it is not surprising that motor impairments, including upper extremity fine motor difficulty (i.e., difficulty with opening jars) and lower extremity gross motor difficulty (i.e., delays or impairments with regard to ambulation) are commonly seen in children with DM1.

Independent walking is typically delayed, but achieved, in the majority of children with DM1 [40–44]. Studies have shown ambulation onset to be between 11 and 60 months of age, with variation based on severity of disease and coexisting foot deformities [40–44]. Delayed ambulation is thought to be multifactorial, due to one or more of the following factors: intellectual disability, muscular weakness, hypotonia, and/or foot deformities [38]. Table 36.2 details the results of studies investigating ambulation in this population [40–44].

Children with congenital DM1 who survive the neonatal period will typically have progressive motor improvement during early childhood; however, in adolescence and young adulthood, clinical features of adult DM1 start to appear, including

Table 36.2 Studies on ambulation in childhood-onset DM1 [40–44]

Reference	Findings regarding ambulation
Reardon et al. (1993) [42]	Reported ambulation status of 69 individuals with congenital DM1: – Median age of onset of ambulation of 27 months overall which was broken down further into children with equinovarus (29 months) and without equinovarus (23 months)
Roig et al. (1994) [43]	In a cohort of 18 individuals with congenital DM1: – Ambulation was delayed an average of 14 months – Earliest age the motor milestone of ambulation was achieved was at 18 months – Children with foot deformities such as pes cavus or equinovarus started ambulating later at 2–5 years of age
Kroksmark et al. (2005) [41]	– 10/13 children with severe congenital DM1 (defined as DM1 diagnosis with symptoms present in utero or at birth + need for resuscitation and/or respiratory assistance at birth) started ambulation at a median age of 22 months (range 13–54 months); 2/10 required assistive devices for ambulating; 2/13, who were aged 10 months and 34 months, had not started ambulating yet – 14/15 children with mild congenital DM1 (defined as DM1 diagnosis with symptoms present in utero or at birth without need for resuscitation and/or respiratory assistance at birth) started ambulation at a median age of 19 months (range 12–43 months); 1/15 had not yet ambulated but was only 10 months old – 14/14 children with childhood DM1 (defined as DM1 diagnosis with symptom onset at 1–10 years old) achieved independent ambulation at a median age of 15 months (range 11–18 months)
Canavese and Sussman (2009) [40]	In a retrospective chart review of 30 children with congenital DM1: – 29/30 children were able to achieve independent walking at a mean age of 29 months (range 14–60 months) – Some children initially required an assistive device for ambulation, but all who initially used an assistive device were able to progress to independent ambulation
Johnson et al. (2014) [44]	A parental survey of the functional impact of DM1 on children with onset prior to age 18 revealed: – While most individuals did not require the use of mobility devices, 23% of youth in the study used ankle or leg bracing, 11% used canes or walkers, 14% used wheelchairs, and 6% used power wheelchairs

ocular involvement with cataracts, progressive motor decline, and muscle wasting [39, 41, 43]. Although motor improvement is seen during childhood, physical impairments are still appreciated throughout childhood. A study comparing children ages 3–13 with congenital DM1 to healthy controls demonstrated longer times in the DM1 group for physical mobility measures of time to climb four stairs, time for 10-m self-selected pace walk, 10-m run, and time rising from the floor from a supine position [45].

Children with childhood-onset DM1 typically have more mild motor impairments than individuals with congenital DM1; however, they also have progressive disease, resulting in classic adult DM1 symptoms in adulthood [41]. In a parental

survey of the functional impact of DM1 on children with onset prior to age 18, hand weakness and difficulty opening jars were commonly reported and hand/finger impairments and myotonia increased with age [44].

Spine Conditions

Neurogenic scoliosis, or neuromuscular scoliosis, is a spinal deformity with three-dimensional components, including a Cobb angle, or frontal plane curve, more than 10° that is secondary to imbalanced trunk musculature control around the spinal axis in neurologic, muscular, or neuromuscular conditions [46]. It can occur from a young age, is typically progressive, and can be associated with kyphosis. It is important to screen for neurogenic scoliosis in children with neuromuscular conditions [46]. Neuromuscular scoliosis or kyphoscoliosis requires close radiologic monitoring, bracing, and in some cases, surgery [40, 46].

Given the neurologic involvement of DM1, it is not surprising that neurogenic scoliosis is a possible comorbidity associated with DM1 [40–43, 47]. Canavese and Sussman's study of orthopedic manifestations of DM1 revealed a 30% rate of either scoliosis or kyphoscoliosis among individuals with congenital DM1 in their institution. The age of onset was 8–10 years old [40]. Schilling et al. reported orthopedic manifestations of DM1 in individuals with congenital and adult-onset DM1. In that study, 3/21 had scoliosis (with Cobb angles of 10, 45, and 100) and 6/21 had hyperkyphosis [47].

Foot Conditions

Congenital talipes equinovarus and other foot deformities are common comorbidities in DM1, particularly congenital DM1. Congenital talipes equinovarus, or clubfoot, is a complex congenital foot deformity with four components: (1) hindfoot equinus, (2) hindfoot varus, (3) midfoot cavus, and (4) forefoot adduction [48]. Congenital talipes equinovarus can be typical or atypical. Typical congenital talipes equinovarus is seen in children without comorbid conditions, while atypical congenital talipes equinovarus can be seen in children with comorbid conditions, such as neurologic conditions like DM1 [49]. An increased incidence of congenital talipes equinovarus has been reported in congenital DM1 [39].

Examples of other foot deformities that have been reported in individuals with DM1 include equinus deformity (ankle plantarflexion contractures), equinovarus deformity (contracture of the foot in both ankle plantarflexion and ankle inversion), and planovalgus deformity (flat feet) [40, 47]. In both the Cavanese and Schilling studies, equinus deformities occurred relatively frequently [40, 47].

Foot deformities should be evaluated by an orthopedic specialist. Congenital talipes equinovarus is typically treated with a special technique of serial casting, called

the Ponsetti Method and may also require surgical correction with Achilles tenotomy or other surgeries [48, 49]. Rapid identification and orthopedic referral is recommended. Treatment of other foot deformities is typically based on the severity of the condition and may include the use of orthotics, stretching, and/or surgery. Again, identification and Orthopedic referral is recommended.

Contractures

Upper and lower extremity muscle contractures can also be associated with DM1 [40, 41, 43, 47]. Contractures refer to the loss of mobility at joints due to structural changes in soft tissues, such as muscles, tendons, and ligaments [50, 55]. Since DM1 predominantly affects distal motor strength, not surprisingly, contractures are also more commonly seen in the distal compared to proximal extremities [47]. Examples of reported contracture types in this population include equinus contractures, equinovarus contractures, hip abduction contractures, hip flexion contractures, knee flexion contractures, shoulder internal rotation contractures, and elbow flexion contractures [40, 47]. Gentle daily stretching is generally recommended to prevent further contracture deformity and to allow flexibility within the range of motion that is allowed at the joint. Strengthening opposing muscle groups is also helpful, as is the use of bracing for positioning and prevention of contracture progression. In situations of fixed contractures unresponsive to conservative measures that cause functional impairments or put the patient at risk for other comorbidities (such as skin breakdown), surgical intervention should be considered [50, 55]. Children with DM1 with contractures should be followed by Rehabilitation Medicine and/or Orthopedics to help guide care.

Lower Extremity Torsion Deformities

Lower extremity torsion deformities are rotational differences of the long bones of the lower extremities. Common examples include femoral anteversion, internal tibial torsion, and external tibial torsion. Femoral anteversion often self-resolves by age 10–12. In cases where it does not resolve and when it is causing functional impairment, surgical correction can be considered. Internal tibial torsion often self-resolves by age 5–6, while external tibial torsion can remain stable or worsen with age. In cases of persistent tibial torsion with related functional impairment, surgery can be considered [51].

Although not classically described as associated comorbidity with myotonic dystrophy, the presence of torsional deformities was noted in some individuals with DM1 in Cavanese and Sussman's study. Three out of 30 individuals with DM1 had femoral anteversion (treated surgically in 2/3 cases with distal femoral rotational osteotomy). One out of 30 had internal tibial torsion treated surgically with distal

tibial rotational osteotomy. One out of 30 had external tibial torsion treated surgically with distal tibial rotational osteotomy [40].

Anesthesia Considerations

When considering Orthopedic or any surgical referral for patients with neuromuscular conditions, such as DM1, it is important to consider the possible risk of anesthesia complications. Certain anesthesia agents, such as thiopentone, halothane, suxamethonium, and neostigmine have been associated with perioperative complications in individuals with DM1; however, there have also been reports of perioperative pulmonary complications outside of the use of these agents due to the known respiratory comorbidities of DM1 [52, 53]. There is a known increased risk of perioperative pulmonary complications in individuals with DM1 [52, 53]. It is therefore important for the anesthesiologist caring for a patient with DM1 to be aware of their diagnosis to best plan for a safe anesthesia experience.

Clinical Pearls

- DM1 has subtypes based on age of onset and severity.
  - Congenital DM1: Hypotonia, generalized weakness, respiratory insufficiency, congenital talipes equinovarus, developmental delays, with eventual progression to adult/classic clinical presentation.
  - Adult/Classic DM1: Facial weakness, distal>proximal weakness, myotonia, cataracts, cardiac conduction abnormalities.
  - Mild/Late-Onset DM1: Presenting symptoms later in life and typically only include myotonia and cataracts.
- DM1 is associated with many systemic manifestations including neurologic, cardiac, respiratory, endocrine, and orthopedic concerns. Although the focus of this chapter is on orthopedic considerations, clinicians should be familiar with the comorbidities presented in Table 36.1.
- Independent walking is typically delayed, but achieved, in the majority of children with congenital DM1.
  - Children may initially require use of an assistive device such as a walker for ambulation assistance, but typically are able to progress to independent ambulation.
  - Delayed ambulation is likely multifactorial, due to one or more of the following factors:

    Intellectual disability
    Muscular weakness

Hypotonia
Foot Deformities

- Neurogenic scoliosis and kyphoscoliosis are not uncommon (30% in one study and 14% in another study), in the school age years in individuals with DM1.
  - This requires radiologic evaluation, referral to an orthopedic specialist, bracing, and possible surgery.
- Foot deformities, such as congenital talipes equinovarus, equinus, equinovarus, planovalgus deformity, or hallus valgus interfalangeus can be seen in individuals with DM1.
  - Treatment of congenital talipes equinovarus typically requires Ponsetti Method casting and possible surgery.
  - Orthopedic referral for congenital talipes equinovarus or other foot deformities should be performed with early recognition of the deformities.
- Contractures are commonly comorbid in individuals with DM1.
  - Daily stretching is recommended for prevention of further deformity.
  - Rehabilitation Medicine and/or Orthopedic referral is important as bracing or surgery is sometimes considered.
- There is an increased risk of perioperative pulmonary complications in individuals with DM1 as well as complications with certain anesthetic agents. It is critical for the anesthesiologist involved in the care of an individual with DM1 to be aware of their diagnosis to prepare for a safe anesthesia experience.

Conclusions

DM1 is a genetic condition with neurologic, respiratory, cardiac, ophthalmologic, endocrine, gastrointestinal, and orthopedic manifestations. Interdisciplinary care is important to provide the best care for these patients. This includes involvement of specialists in the disciplines of Neurology, Rehabilitation Medicine, Cardiology, Pulmonary, Orthopedics, Ophthalmology, and, at times, Gastroenterology and/or General Surgery. Cardiorespiratory concerns are of particular concern as cardiorespiratory conditions are the most common cause of death in DM1. Orthopedic conditions include foot deformities (such as congenital talipes equinovarus), contractures, neurogenic scoliosis, and/or lower extremity torsional deformities. Involvement of Rehabilitation Medicine and Orthopedics in the management of these orthopedic concerns can be helpful for improvement in functional outcomes.

References

1. Preston DC, Shapiro BE. Electromyography and neuromuscular disorders: clinical-electrophysiological correlations. Elsevier Saunders. 2013.
2. Bird TD. Myotonic dystrophy type 1. Seattle: University of Washington; 1993.
3. Hahn C, Salajegheh MK. Myotonic disorders: a review article. Iran J Neurol. 2016;15:46–53.
4. Emery AE. Population frequencies of inherited neuromuscular diseases—a world survey. Neuromuscul Disord. 1991;1:19–29.
5. Alexander MA, Matthew DJ. Pediatric rehabilitation, Fifth Edition: Principles and practice. Demos Medical Publishing; 2015. p. 636.
6. Meola G, Cardani R. Myotonic dystrophies: an update on clinical aspects, genetic, pathology, and molecular pathomechanisms. Biochim Biophys Acta Mol basis Dis. 2015;1852:594–606.
7. Hunter A, Tsilfidis C, Mettler G, Jacob P, Mahadevan M, Surh L, Korneluk R. The correlation of age of onset with CTG trinucleotide repeat amplification in myotonic dystrophy. J Med Genet. 1992;29:774–9.
8. Melacini P, Villanova C, Menegazzo E, et al. Correlation between cardiac involvement and CTG trinucleotide repeat length in myotonic dystrophy. J Am Coll Cardiol. 1995;25:239–45.
9. De Antonio M, Dogan C, Hamroun D, Mati M, Zerrouki S, Eymard B, et al. Unravelling the myotonic dystrophy type 1 clinical spectrum: a systematic registry-based study with implications for disease classification. Rev Neurol (Paris). 2016;172:572–80.
10. Dogan C, De Antonio M, Hamroun D, et al. Gender as a modifying factor influencing myotonic dystrophy type 1 phenotype severity and mortality: a nationwide multiple databases cross-sectional observational study. PLoS One. 2016;11:e0148264.
11. Johnson ER, Abresch RT, Carter GT, Kilmer DD, Fowler WM, Sigford BJ, Wanlass RL. Profiles of neuromuscular diseases. Myotonic dystrophy. Am J Phys Med Rehabil. 1995;74:S104–16.
12. Hogrel JY, Ollivier G, Ledoux I, Hébert LJ, Eymard B, Puymirat J, Bassez G. Relationships between grip strength, myotonia, and CTG expansion in myotonic dystrophy type 1. Ann Clin Transl Neurol. 2017;4:921–5.
13. Chong-Nguyen C, Wahbi K, Algalarrondo V, et al. Association between mutation size and cardiac involvement in myotonic dystrophy type 1. Circ Cardiovasc Genet. 2017;10(3):e001526.
14. Quera Salva MA, Blumen M, Jacquette A, Durand MC, Andre S, De Villiers M, et al. Sleep disorders in childhood-onset myotonic dystrophy type 1. Neuromuscul Disord. 2006;16:564–70.
15. Meola G. Myotonic dystrophy is not only a disease affecting the muscles, it is also a CNS disorder. Eur J Neurol. 2014;21:183–4.
16. Ekström AB, Hakenäs-Plate L, Tulinius M, Wentz E. Cognition and adaptive skills in myotonic dystrophy type 1: a study of 55 individuals with congenital and childhood forms. Dev Med Child Neurol. 2009;51:982–90.
17. Douniol M, Jacquette A, Cohen D, et al. Psychiatric and cognitive phenotype of childhood myotonic dystrophy type 1. Dev Med Child Neurol. 2012;54:905–11.
18. Angeard N, Huerta E, Jacquette A, Cohen D, Xavier J, Gargiulo M, et al. Childhood-onset form of myotonic dystrophy type 1 and autism spectrum disorder: is there comorbidity? Neuromuscul Disord. 2018;28:216–21.
19. Melacini P, Buja G, Fasoli G, Armani M, Scognamiglio R, Volta D. The natural history of cardiac involvement in myotonic dystrophy: an eight-year follow-up in 17 patients*. Clin Cardiol. 1988;11(4):231–8.
20. Melacini P, Egloff C, Armani M, Miraglia G, Angelini C, Marinato PG, Buja GF. Atrioventricular conduction system in myotonic dystrophy: value of electrophysiological investigation. Acta Neurol (Napoli). 1981;3:396–400.

21. Cudia P, Bernasconi P, Chiodelli R, et al. Risk of arrhythmia in type I myotonic dystrophy: the role of clinical and genetic variables. J Neurol Neurosurg Psychiatry. 2009;80:790–3.
22. Valaperta R, De Siena C, Cardani R, et al. Cardiac involvement in myotonic dystrophy: the role of troponins and N-terminal pro B-type natriuretic peptide. Atherosclerosis. 2017;267:110–5.
23. Chong-Nguyen C, Wahbi K, Algalarrondo V, et al. Association between mutation size and cardiac involvement in myotonic dystrophy type 1: an analysis of the DM1-heart registry. Circ Cardiovasc Genet. 2017;10:1–8.
24. Nugent A-M, Smith IE, Shneerson JM. Domiciliary-assisted ventilation in patients with myotonic dystrophy. Chest. 2002;121:459–64.
25. Boussaïd G, Wahbi K, Laforet P, Eymard B, Stojkovic T, Behin A, et al. Genotype and other determinants of respiratory function in myotonic dystrophy type 1. Neuromuscul Disord. 2018;28:222–8.
26. Ikeda KS, Iwabe-Marchese C, França MC Jr, Nucci A, Carvalho KM. Myotonic dystrophy type 1: frequency of ophthalmologic findings. Arq Neuropsiquiatr. 2016;74:183–8.
27. Takeshima K, Ariyasu H, Ishibashi T, Kawai S, Uraki S, Koh J, et al. Myotonic dystrophy type 1 with diabetes mellitus, mixed hypogonadism and adrenal insufficiency. Endocrinol Diabetes Metab Case Rep. 2018;2018:17-0143. https://doi.org/10.1530/EDM-17-0143. eCollection 2018.
28. Johnson NE, Butterfield R, Berggren K, et al. Disease burden and functional outcomes in congenital myotonic dystrophy: a cross-sectional study. Neurology. 2016;87:160–7.
29. Smith CA, Gutmann L. Myotonic dystrophy type 1 management and therapeutics. Curr Treat Options Neurol. 2016;18:52.
30. Gallais B, Gagnon C, Mathieu J, Richer L. Cognitive decline over time in adults with myotonic dystrophy type 1: a 9-year longitudinal study. Neuromuscul Disord. 2017;27:61–72.
31. Choudhary P, Nandakumar R, Greig H, Broadhurst P, Dean J, Puranik R, et al. Structural and electrical cardiac abnormalities are prevalent in asymptomatic adults with myotonic dystrophy. Heart. 2016;102:1472–8.
32. Zanigni S, Evangelisti S, Giannoccaro MP, et al. Relationship of white and gray matter abnormalities to clinical and genetic features in myotonic dystrophy type 1. NeuroImage Clin. 2016;11:678–85.
33. Meola G, Cardani R. Myotonic dystrophy type 2: an update on clinical aspects, genetic and pathomolecular mechanism. J Neuromuscul Dis. 2015;2:S59–71.
34. Theadom A, Rodrigues M, Roxburgh R, Balalla S, Higgins C, Bhattacharjee R, et al. Prevalence of muscular dystrophies: a systematic literature review. Neuroepidemiology. 2014;43:259–68.
35. Caso F, Agosta F, Peric S, Rakočević-Stojanović V, Copetti M, Kostic VS, Filippi M. Cognitive impairment in myotonic dystrophy type 1 is associated with white matter damage. PLoS One. 2014;9:e104697.
36. Kamsteeg E-J, Kress W, Catalli C, Hertz JM, Witsch-Baumgartner M, Buckley MF, et al. Best practice guidelines and recommendations on the molecular diagnosis of myotonic dystrophy types 1 and 2. Eur J Hum Genet. 2012;20:1203–8.
37. Udd B, Krahe R. The myotonic dystrophies: molecular, clinical, and therapeutic challenges. Lancet Neurol. 2012;11:891–905.
38. Turner C, Hilton-Jones D. The myotonic dystrophies: diagnosis and management. J Neurol Neurosurg Psychiatry. 2010;81:358–67.
39. Harper PS, Brook JD, Newman E. Myotonic dystrophy. London: W.B. Saunders; 2001.
40. Canavese F, Sussman MD. Orthopaedic manifestations of congenital myotonic dystrophy during childhood and adolescence. J Pediatr Orthop. 2009;29:208–13.
41. Kroksmark AK, Ekström AB, Björck E, Tulinius M. Myotonic dystrophy: muscle involvement in relation to disease type and size of expanded CTG-repeat sequence. Dev Med Child Neurol. 2005;47:478–85.
42. Reardon W, Newcombe R, Fenton I, Sibert J, Harper PS. The natural history of congenital myotonic dystrophy: mortality and long term clinical aspects. Arch Dis Child. 1993;68:177–81.

43. Roig M, Balliu PR, Navarro C, Brugera R, Losada M. Presentation, clinical course, and outcome of the congenital form of myotonic dystrophy. Pediatr Neurol. 1994;11:208–13.
44. Johnson NE, Luebbe E, Eastwood E, Chin N, Moxley RT, Heatwole CR. The impact of congenital and childhood myotonic dystrophy on quality of life: a qualitative study of associated symptoms. J Child Neurol. 2014;29:983–6.
45. Pucillo EM, Dibella DL, Hung M, Bounsanga J, Crockett B, Dixon M, et al. Physical function and mobility in children with congenital myotonic dystrophy. Muscle Nerve. 2017;56:224–9.
46. Paulson A. Neurogenic scoliosis. In: PM&R Knowl. Now; 2018. https://now.aapmr.org/neurogenic-scoliosis/. Accessed 13 Nov 2018.
47. Schilling L, Forst R, Forst J, Fujak A. Orthopaedic disorders in myotonic dystrophy type 1: descriptive clinical study of 21 patients. BMC Musculoskelet Disord. 2013;14:338.
48. Ganesan B, Luximon A, Al-Jumaily A, Balasankar SK, Naik GR. Ponseti method in the management of clubfoot under 2 years of age: a systematic review. PLoS One. 2017;12:e0178299.
49. Staheli L, et al. Clubfoot: ponseti management. 3rd ed. Global Health Organization; 2009. p. 32.
50. Cristian A, Khanna A, Kim R. Contractures. In: PM&R Knowl. Now; 2014. https://now.aapmr.org/contractures/. Accessed 13 Nov 2018.
51. Smith BG. Lower extremity disorders in children and adolescents. Pediatr Rev. 2009;30:287–93; quiz 294.
52. Mathieu J, Allard P, Gobeil G, Girard M, De Braekeleer M, Bégin P. Anesthetic and surgical complications in 219 cases of myotonic dystrophy. Neurology. 1997;49:1646–50.
53. Rosenbaum HK, Miller JD. Malignant hyperthermia and myotonic disorders. Anesthesiol Clin North Am. 2002;20:623–64.
54. Mcdonald CM. Clinical approach to the diagnostic evaluation of hereditary and acquired neuromuscular diseases. Phys Med Rehabil Clin N Am. 2012;23(3):495–563.
55. Farmer SE, James M. Contractures in orthopaedic and neurological conditions: a review of causes and treatment. Disabil Rehabil. 2001;23(13):549–58.

Chapter 37
Nutritional and Genetic Rickets

Alicia C. Zolkoske

Introduction

The incidence of nutritional rickets in the United States is 24 cases per 100,000 [1].

Nutritional Rickets generally results from deficiency in dietary intake of Vitamin D, calcium, or a combined deficiency. There have been rare cases of nutritional rickets due to phosphate deficiency in the setting of low phosphate containing breastmilk or with Neocate formula [2].

Vitamin D status is best assessed by measuring serum concentrations of 25-hydroxyVitamin D (25OHD). The Global Consensus Recommendations define Vitamin D deficiency as a serum 25OHD concentration less than 12 nanograms/milliliter (ng/mL) (30 nanomoles/liter [nmol/L]), and insufficiency as 12–20 ng/mL (30–50 nmol/L) [3].

Risk factors for nutritional rickets include infants exclusively breastfed without Vitamin D supplementation, infants born to mothers with Vitamin D deficiency, insufficient dietary intake of Vitamin D, limited exposure to sunlight, and dark skin pigmentation. Sunlight is required for conversion of cholesterol to Vitamin D. This conversion is decreased in individuals with darker pigmented skin (Fig. 37.1).

The half-life of 25OHD in an infant is approximately 2–3 weeks after birth [4]. Vitamin D deficiency may also occur in individuals with concurrent malabsorptive conditions such as cystic fibrosis, inflammatory bowel disease, or following gastric/intestinal resection surgery.

A. C. Zolkoske (✉)
Department of Orthopedic Surgery, Children's Hospital of Wisconsin/Medical College of Wisconsin, Milwaukee, WI, USA
e-mail: azolkoske@chw.org

J. F. Sarwark, R. L. Carl (eds.), *Orthopaedics for the Newborn and Young Child*,
https://doi.org/10.1007/978-3-031-11136-5_37

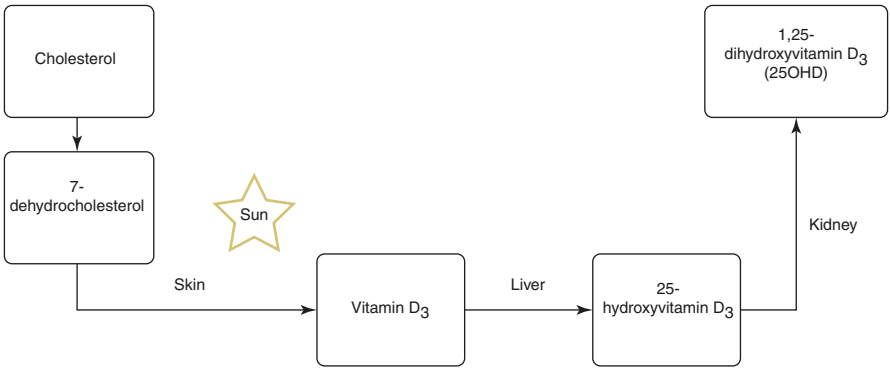


Fig. 37.1 Importance of the sun

Sources of Vitamin D include fortified infant formulas, fortified milk, fortified cereals and juices, as well as some fish such as salmon [1]. According to the Food and Drug Administration Standard of Identity for Milk, milk should contain 400 IU per quart if Vitamin D is added [5].

Pathophysiology

Nutritional rickets is a disorder characterized by defective chondrocyte differentiation, mineralization of the growth plate, and defective osteoid mineralization [3].

Vitamin D deficiency impairs intestinal absorption of calcium. With insufficient serum calcium concentration caused by either Vitamin D deficiency or inadequate dietary calcium intake, parathyroid hormone will stimulate osteoclastic bone resorption to release stored calcium from bone and maintain normal serum calcium [6]. Bone resorption also leads to increased alkaline phosphatase levels. Bone disease develops in setting of resorption and is notable once elevated parathyroid hormone has led to low serum phosphate levels [7]. Eventually, serum calcium levels decrease as increasing parathyroid hormone is no longer able to compensate for decreased absorption.

Laboratory analysis allows further delineation of the etiology of rickets. Varying severities of Vitamin D deficiency present with alteration of other laboratory values, such as alkaline phosphatase and parathyroid hormone (Table 37.1). Elevated alkaline phosphatase activity confirms the diagnosis of rickets in patients with suspicious radiographic findings [8].

Table 37.1 Vitamin D. Deficiencies

Vitamin D deficiency	Calcium	Phosphorus	Alkaline phosphatase	25-OHD	1,25-OHD	Parathyroid hormone
Mild	Decreased/ normal	Decreased/ normal	Elevated	Decreased	Normal	Normal
Moderate	Decreased/ normal	Decreased	Markedly elevated	Decreased	Normal	Elevated
Severe	Decreased	Decreased	Markedly elevated	Markedly decreased	Decreased	Markedly elevated

Clinical Findings

While multiple systems of the body may be affected in children with nutritional rickets, there are specific skeletal manifestations that can be characterized on X-ray. These include:

- Irregular calcification
- Metaphyseal cupping
- Frayed/Widened physis
- Osteomalacia
- Rachitic rosary (enlargement of costochondral junction) (Fig. 37.2)

Pathologic fractures on X-ray may also be suggestive of nutritional rickets. Of note, children with radiographically confirmed rickets have an increased risk of fracture whereas children with isolated Vitamin D deficiency without corresponding radiographic abnormalities are not at increased risk of fracture [3].

Additional clinical exam findings suggestive of rickets include [9]:

- Frontal bossing
- Delayed fontanelle closure
- Flared wrists/ankles
- Genu valgum/genu varum
- Hypotonia

Other health complications may consist of seizures, tetany, and cardiac arrhythmias secondary to hypocalcemia, bone pain and muscle weakness, dental abnormalities, and developmental delays [1]. Associated derangement in calcium may have devastating effects, including death from heart failure caused by hypocalcemic cardiomyopathy [10].

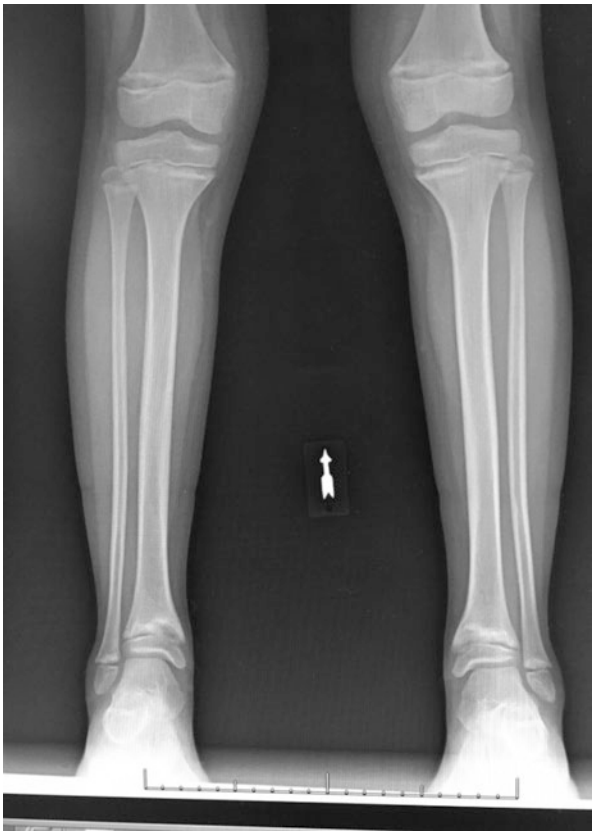


Fig. 37.2 Mild physeal widening and irregularity with sclerosis in a 10-year-old female with rickets

Recommendations

The American Academy of Pediatrics most recent statement on prevention and management of rickets reports that infants up to 12 months of age require 400 international units (IU) of Vitamin D daily while older children/adolescents require 600 IU daily [1]. Exclusively breastfed infants should initiate supplementation with 400 IU of Vitamin D within a few days of life. This should continue until they are at least 1 year of age [1].

Treatment

The Global Consensus Recommendations state that children with nutritional rickets due to Vitamin D deficiency should receive at least 2000 IU of Vitamin D daily for 3 months, after which a 25OHD concentration should be repeated to determine whether supplementation should be continued. Treatment of nutritional rickets should include at least 500 milligrams of calcium daily through diet or supplementation, in addition to Vitamin D supplementation [3].

Genetic Forms of Rickets

Genetic rickets: two types—hypophosphatemic and Vitamin D dependent.

In addition to nutritional rickets, there are many genetic forms of rickets. Genetic forms of rickets can be grouped into two types: hypophosphatemic rickets (also referred to as vitamin D-resistant rickets) and vitamin D-dependent rickets [11].

Hypophosphatemic Rickets

The category of hypophosphatemic rickets involves a group of disorders characterized by abnormalities of the renal tubules leading to decreased phosphate reabsorption in the kidneys. Mutations in one of several genes, including phosphate-regulating neutral endopeptidase (PHEX) and Fibroblast growth factor 23 (FGF 23), can cause inadequate phosphate reabsorption. The classic form of hypophosphatemic rickets is X-linked hypophosphatemia (XLH) caused by PHEX mutations, but there are autosomal recessive (caused by FGF23 mutations) and autosomal dominant forms [11].

Individuals with hypophosphatemic rickets typically have hypercalciuria, normal serum calcium, hypophosphatemia, and elevated alkaline phosphatase and parathyroid hormone.

Labs: Calcium is usually normal (it is getting leached out of bones), Phosphate low, Alk phos and PTH high. Patients with hypophosphatemic rickets are treated with phosphate and calcitriol.

Rickets can also be associated with McCune Albright Syndrome. Children with McCune Albright have polyostotic fibrous dysplasia, café au lait birthmarks, and precocious puberty. Rickets, when present, tends to occur later in childhood and treatment is the same as with hypophosphatemic rickets [12].

Vitamin D-Dependent Rickets (VDDR)

Vitamin D-dependent rickets results from abnormalities of Vitamin D receptors or from abnormalities of enzymes involved in vitamin D production.

Types of VDDR

1. VDDR1A—Autosomal recessive (AR) disorder due to an abnormality in CYP27B1 gene for 1 alpha hydroxylase. This mutation leads to failure of hydroxylation of 25(OH) Vitamin D. Affected individuals have high 25(OH) Vitamin D and low 1,25(OH) Vitamin D. Treatment is with calcitriol (1,25-dihydroxyvitamin D3) and oral calcium.

2. VDDR1B—AR disorder due to abnormality in CYP2R1 gene encoding 25-hydroxylase leads to low 25(OH) Vitamin D. Treatment is with calcitriol.
3. VDDR2A—AR disorder due to an abnormality in the VDR Gene encoding Vitamin D receptor. Affected individuals have high 1,25(OH) Vitamin D. Alopecia is associated with this type of rickets. Treatment is with high doses of calcitriol and calcium.
4. VDDR2B—Very rare form of VDDR caused by excessive expression of proteins that affect vitamin D binding to the vitamin D receptor. This type is similar to VDDR2A in clinical presentation (including alopecia) and treatment [13].

References

1. Folson L, DiMeglio L. Recommendations released on prevention, management of rickets. AAP News. Epub 2017 Feb 10. http://www.aappublications.org/news/2017/02/10/Rickets021017.
2. Gonzalez Ballesteros LF, Ma N, Ward L, Backeljauw P, Wasserman H, Weber D, DiMeglio L, et al. Hypophosphatemia associated with elemental formula use in children with feeding problems. In Annual meeting of the pediatric academic societies, Baltimore, MD. May 2016. Abstract #3853.
3. Munn CF, Shaw N, Kiely M, Specker BL, Thacher TD, Ozono K, et al. Global consensus recommendations of prevention and management of nutritional rickets. J Clin Endocrinol Metab. 2016;101(2):394–415. Epub 2016 Jan 8.
4. Misra M, Pacaud D, Petryk A, Collett-Solberg PF, Kappy M. Vitamin D deficiency in children and its management: review of current knowledge and recommendations. Pediatrics. 2008;122(2):398.
5. Holick MF, Shao Q, Liu WW, Tai C. The Vitamin D content of fortified mild and infant formula. N Engl J Med. 1992;326:1178–81.
6. Thacher TD, Clarke BL. Vitamin D insufficiency. Mayo Clin Proc. 2011;86(1):50–60.
7. Tiosano D, Hochberg Z. Hypophosphatemia: the common denominator of all rickets. J Bone Miner Metab. 2009;27(4):392–401.
8. Lambert AS, Linglart A. Hypocalcaemic and hypophosphatemic rickets. Best Pract Res Clin Endocrinol Metab. 2018;32(4):455–76.
9. Thandrayen K, Pettifor JM. The roles of Vitamin D and dietary calcium in nutritional rickets. Bone Rep. 2018;8:81–9.
10. Maiya S, Sullivan I, Allgrove J, et al. Hypocalcaemia and Vitamin D deficiency: an important, but preventable, cause of life-threatening infant heart failure. Heart. 2008;94(5):581–4.
11. Carpenter TO. The expanding family of hypophosphatemic syndromes. J Bone Miner Metab. 2012;30(1):1–9.
12. POLYOSTOTIC FIBROUS DYSPLASIA, INCLUDED; PFD, INCLUDED; POFD, INCLUDED. Johns Hopkins University. Online Mendelian Inheritance in Man (OMIM) Web site. Accessed 16 Oct 2019.
13. Acar S, Demir K, Shi Y. Genetic causes of rickets. J Clin Res Pediatr Endocrinol. 2017;9(Suppl 2):88–105.

Chapter 38
Osteogenesis Imperfecta

Srirupa Hari Gopal and Merritt E. Adams

Abbreviations

BMD	Bone mineral density
BMP	Bone morphogenic protein
CRTAP	Cartilage-associated Protein
CYPB/PPIB	Cyclophilin-B
DEXA	Dual Energy X-ray Absorptiometry
FKB10	FK506 Binding Protein
IFITM-5	Interferon-induced transmembrane protein-5
LEPRE1	Leprecan-like protein 1
OI	Osteogenesis Imperfecta
SERPINF1	Serpin family F Member 1
SERPINH1	Serpin Family H Member 1
SP7	Specificity Protein-7

S. H. Gopal
Department of Pediatrics, Erlanger Hospital, University of Tennessee College of Medicine at Chattanooga, Chattanooga, TN, USA
e-mail: srirupa.harigopal@erlanger.org

M. E. Adams (✉)
Department of Orthopedic Surgery, Children's Hospital at Erlanger, UT College of Medicine Chattanooga, Chattanooga, TN, USA
e-mail: merritt.adams@erlanger.org

J. F. Sarwark, R. L. Carl (eds.), *Orthopaedics for the Newborn and Young Child*,
https://doi.org/10.1007/978-3-031-11136-5_38

Introduction

Osteogenesis Imperfecta (OI), also called "Brittle bone disease," is a heterogenous group of a rare inherited disorder of the connective tissue, causing excessive fragility of bones. As the name suggests, patients with this disorder have "imperfect bones" that are highly susceptible to fracture with minor or no trauma. In some cases, fractures occur even before birth. Other clinical features of OI include blue sclera, short stature, macrocephaly, hearing loss, cardiac, and neurological complications.

The original classification of osteogenesis imperfecta by David Sillence in 1979 was based on autosomal dominant defects in genes COL1A1 and COL1A2—which encode the proteins that makeup type 1 collagen. Autosomal recessive types of Osteogenesis Imperfecta have subsequently been discovered and affect genes involved in posttranslational modification and folding of collagen thus affecting the overall quality of collagen [1].

Epidemiology/Pathophysiology

Osteogenesis Imperfecta falls under the category of "orphan disorders" with a prevalence estimate of 6–7 per 100,000 people worldwide. The estimated incidence of OI is approximately 1 per 20,000 births. There is no preferential distribution of autosomal dominant osteogenesis imperfecta by gender, race, or ethnic group [2].

OI is caused most commonly by autosomal dominant mutations in the collagen type 1 alpha 1 and collagen type 1 alpha 2 genes (*COL1A1* and *COL1A2*), which encode the alpha 1 and alpha 2 chains of the type 1 procollagen, respectively. This quantitative defect in the production of type 1 procollagen is responsible for the fragility of bone and subsequent fractures. Type I collagen fibers are polymers of tropocollagen molecules, each of which forms a triple helix consisting of one alpha 2 and two alpha 1 polypeptide chains. The etiology of the autosomal recessive types of OA affects posttranslational modifications of type 1 collagen molecules such as cross-linking, hydroxylation, and mineralization [3]. Recent molecular studies have also revealed that a dextro-rotated triplet structure of glycine-proline-hydroxyproline is vital for the proper folding and stability of the peptide chains. Mutations disrupting this triplet can cause instability of the type 1 collagen. Proteins such as Cartilage-associated protein (CRTAP), Proly-13 hydroxylase 1 (P3H1/LEPRE1), and Cyclophilin B (CyPB/PPIB) play an important role in the maintenance of this triplet structure [4]. Recent research into the genetic variability of OI has led to the discovery of several additional mutations causing severe recessive forms of the disease.

Classification and Clinical Features

Table 38.1 shows the classification of OI. The features of OI vary based on genetic mutations and may vary within affected families. Table 38.2 shows the features of different types of OI. The Original Sillence classification of OI was developed in 1979. Osteogenesis imperfecta was broadly classified OI into four categories based on clinical and radiological features [5]:

1. Dominantly inherited OI with blue sclerae,
2. Lethal perinatal OI with radiographically crumpled femora and beaded ribs,
3. Progressively deforming OI, and
4. Dominantly inherited OI with normal sclerae.

Figures 38.1, 38.2, and 38.3 show features of type 2 OI.

Table 38.1 Classification of OI-genotype and phenotype. Adapted from [6]

Type of OI	Type of inheritance	Gene involved	Effect of gene defect
Type I	AD	COL1A1/COL1A2	Defect in quantity of collagen
Type II	AD	COL1A1/COL1A2	Defect in collagen structure
Type III	AD	COL1A1/COL1A2	Defect in collagen structure
Type IV	AD	COL1A1/COL1A2	Defect in collagen structure
Type V	AD	IFITM-5	Defect in mineralization
Type VI	AR	SERPINF1	Abnormal lamellation
Type VII	AR	CRTAP	Defects in prolyl 3 hydroxylation complex
Type VIII	AR	LEPRE1	Defects in prolyl 3 hydroxylation complex
Type IX	AR	Cyclophilin B (PPIB)	Defects in prolyl 3 hydroxylation complex
Type X	AR	SERPINH1	Defects in collagen chaperones/folding proteins
Type XI	AR	FKBP10	Defects in collagen chaperones/folding proteins
Type XII	AR	SP7	Osteoblast development
Type XIII	AR	BMP1	Defects in collagen processing

Table 38.2 Clinical features of various types of OI

Type of OI	Orthopedic features	Other clinical features
Type I (Lobstein's disease)	Anterior and lateral bowing of Tibia, increased risk of fractures and osteoporosis; Scoliosis and Kyphosis	Postnatal growth deficiency, dentinogenesis imperfecta, irregular placement of teeth and late eruption, hearing impairment due to osteosclerosis, easy bruisability, blue sclera
Type II (Vrolik's disease)	Soft calvarium, multiple wormian bones, shallow orbits, ribbon like long bones-frog leg position, Multiple fractures and callous formation	Prenatal growth deficiency, deep blue sclera, low nasal bridge, hydrops fetalis

(continued)

Table 38.2 (continued)

Type of OI	Orthopedic features	Other clinical features
Type III	Pectus carinatum, kyphoscoliosis, bowing of long bones, progressive bone deformities, macrocephaly	Hearing loss, dentinogenesis imperfecta, triangular facies
Type IV	Brittle bones, femoral bowing of newborn—but may strengthen with time, scoliosis, osteoporosis	Normal sclera, ± dentinogenesis imperfecta
Type V	Frequent fractures, hypertrophic callous formation, restricted supination and pronation, moderate deformities	Normal sclera, ligament laxity. Easy bruisability
Type VI	Moderate to severe deformity, fish-scale appearance of bone under polarized light	Moderate short stature, ligamentous laxity, white or faintly blue sclera, no dentinogenesis imperfecta
Type VII	Limb deformities at birth, normal head circumference, coxa vara	Exophthalmia, white/light blue sclera
Type VIII	Rhizomelia, osteoporosis, under-tubulated long bones	Extreme short stature, white sclera,
Type IX	Moderately severe osteoporosis, no Rhizomelia	Moderate short stature, white sclera
Type X	Bone deformities, multiple fractures, osteopenia	Dentinogenesis imperfecta, blue sclera
Type XI	Progressive kyphoscoliosis, coxa vara, wedge vertebra, wormian bones	White sclera, ligamentous laxity, normal hearing; Bruck syndrome: Severe OI with congenital contractures
Type XII	Moderate bone dysplasia, generalized osteoporosis, bowing of long bones	Normal hearing and normal sclera, joint hyperextensibility
Type XIII	High bone mass, moderate to severe bone deformity, long bone bowing	White sclera, joint hyperextensibility, hypotonia

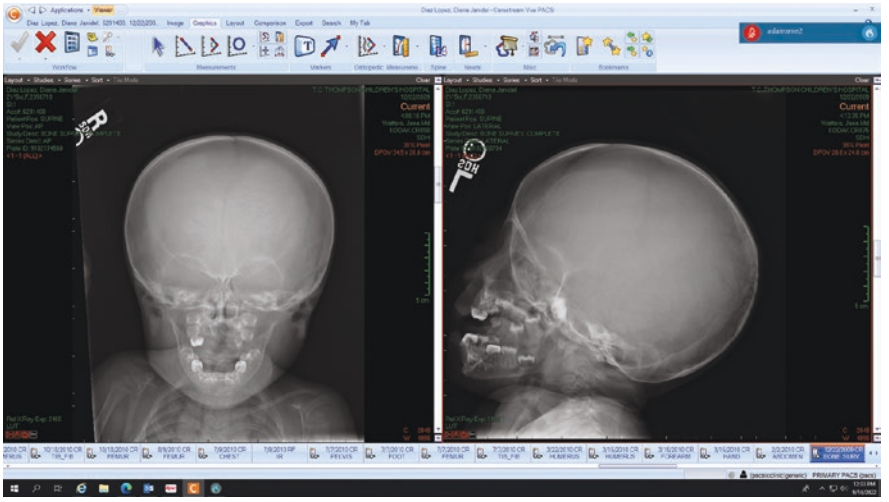


Fig. 38.1 Wormian bones seen in two patients with type 2 OI

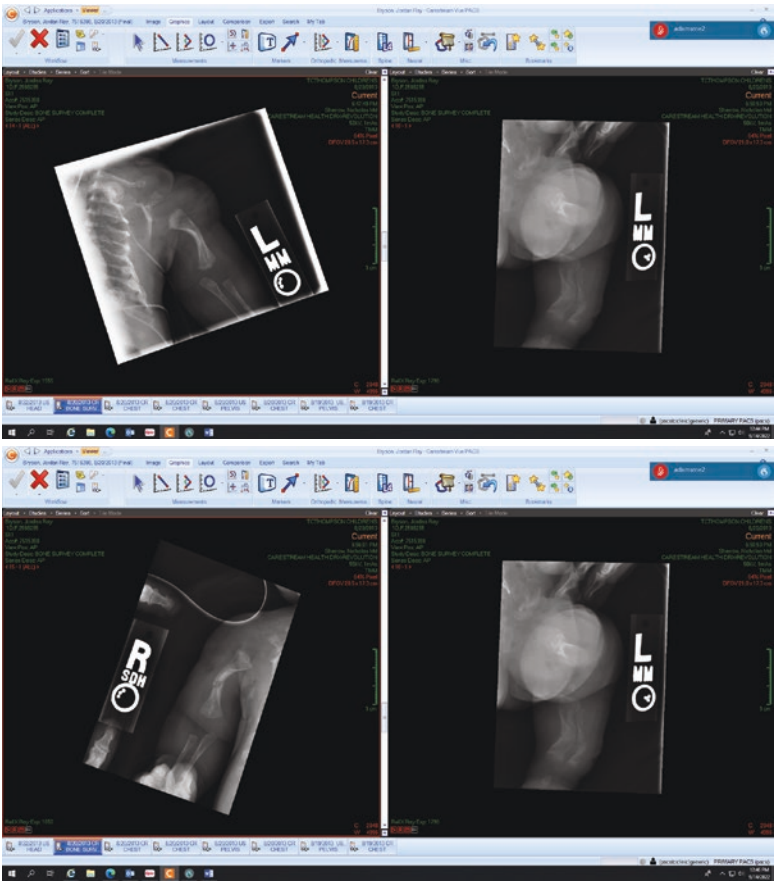


Fig. 38.2 Common features of type 2 OI, showing B/L humeral bowing, beaded ribs, and right humerus fracture

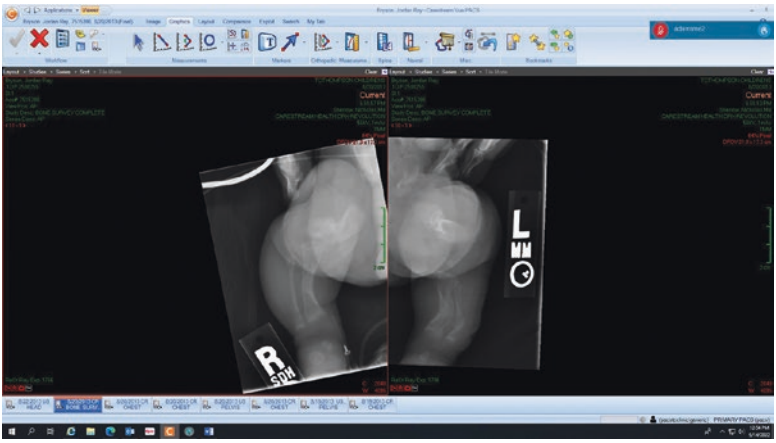


Fig. 38.3 B/L Lower extremities in a patient with type 2 OI showing severe bone deformities

Diagnostic Workup and Differential Diagnosis

Osteogenesis imperfecta is a disorder that can be solely diagnosed based on clinical features. A thorough history and physical examination, primarily focusing on skeletal system can serve as a guide for the diagnosis of OI. Positive family history for diagnosed osteogenesis imperfecta, recurrent fractures, fractures with minimal trauma, easy bruising, short stature, and bone deformities should raise suspicion for OI [7].

A radiographic skeletal survey may show features such as multiple bone fractures with various stages of callous formation, deformities of spine and long bones, increased curvature of long bones, significant osteoporosis, metaphyseal flare, and sharpness of growth plate. In individuals with OI type III, radiographs may show "popcorn" calcifications due to disorganization around the growth plate [8].

If there is a positive family history for osteogenesis imperfecta, routine prenatal ultrasound and genetic testing can be very useful. Ultrasound is helpful in the diagnosis of type II. With Type I and III, prenatal ultrasounds are typically normal. Common indicators of possible OI on prenatal ultrasound include skeletal hypoechogenicity, shortening of bones, abnormal bony curvature, multiple fractures, beading of ribs, and wrinkly appearance of bones [9]. Collagen analysis from the fibroblasts obtained through skin biopsy has been used for the diagnosis of OI. In addition, gene sequence analysis of specific genes such as COL1A1/COL1A2, CRTAP, and LEPRE1 can also help in the diagnosis of specific type of OI.

While children with mild cases of Type I OI may have normal bone mineral density, osteoporosis is a common feature seen in individuals with OI types II, III, and IV. Therefore, dual-energy x-ray absorptiometry (DXA) to evaluate bone mineral density may aid in the diagnosis and management of children with more severe types of OI.

In children with OI, calcium levels are normal in patients and vitamin D levels are variable. However, markers of bone turnover such as osteocalcin, alkaline phosphatase, and amino-terminal telopeptide of type 1 collagen may be useful for monitoring patients with OI [10].

The differential diagnosis for possible OI seen on prenatal ultrasounds includes hypophosphatasia, thanatophoric dysplasia, campomelic dysplasia, and achondrogenesis. All of these conditions can present with rhizomelia and relative macrocephaly. For infants suspected of having OI, non-accidental trauma should be part of the differential diagnosis. Sometimes, both may coexist in the same patient. Thorough history taking and physical examination can help in making the diagnosis. Other differentials include Bruck syndrome, Cole-Carpenter syndrome, infantile hypophosphatasia, and osteoporosis pseudoglioma syndrome [11].

Treatment/Management

The primary goal of management for patients with OI is to decrease bone pain and fragility, increase mobility, and decrease disabilities in activities of daily living. Like any other disorder, the degree of intervention depends on the disability and severity of the disease at presentation.

Physical Rehabilitation

Early intervention programs to manage proper head support, custom molded car seats, proper limb positioning, physical, and occupational therapy for strengthening muscles with isotonic exercises and hydrotherapy can be helpful to improve mobility and prevent injury in infants and young children with more severe types of OI. Evaluation by a physiatrist with experience in prescribing mobility aids, including wheelchairs may also be helpful based on an individual patient's needs [12].

Surgical Management

Surgical intervention may be required to treat certain types of fractures and to correct deformities in patients with OI. Some patients undergo surgery to place intermedullary rods in long bones for prevention of fractures. Early mobilization after surgery is particularly important to prevent bone loss secondary to inactivity. Scoliosis in OI cannot be managed with bracing. Spinal fusion using hooks and wires is avoided due to high risk of complications; however, effective and safer management with pedicle screw instrumentation have been studied [13] (see Fig. 38.4a and b).

Pharmacotherapy

Medical management with intravenous bisphosphonates is currently one of the mainstays of treatment for children with moderate to severe OI. Bisphosphonates help in increasing bone mineral density and prevent the loss of existing bone.

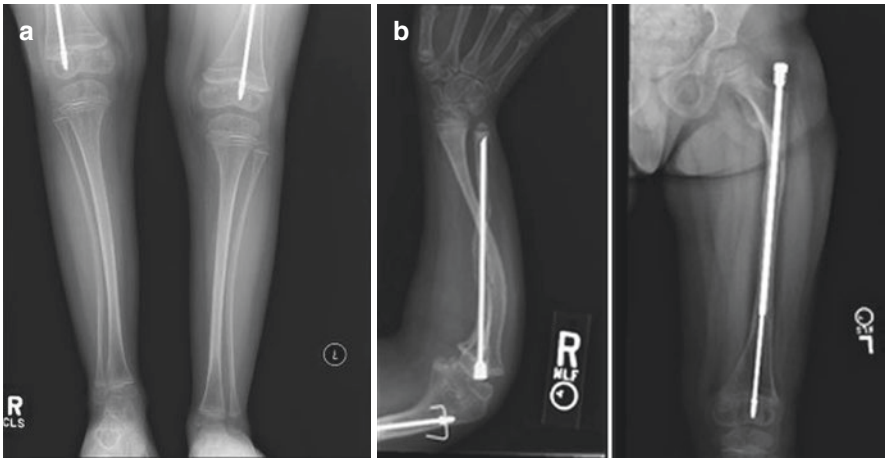


Fig. 38.4 Intermedullary rods done in a patient with type 3 OI. Deformity and malalignment seen in images (**a** and **b**)

Cyclical infusion of Pamidronate is currently the most common medical treatment for patients with OI [11]. Children with OI who used pamidronate showed an increased bone mineral density, improved mobility, ambulation, and pain and reduced fracture rate [14, 15]. Neridronate, an amino bisphosphonate has been investigated extensively and found to induce rapid increase in bone mineral density and, in one study, led to a 64% decrease in fractures [16]. This has been studied in both neonates and adults. Neridronate has been shown to be as efficient as pamidronate in improving vertebral indices. The property of Neridronate that makes it more beneficial is its route of administration—It can be administered both intravenously and intramuscularly thus reducing hospital stay for therapy and helpful for home care [16, 17]. A widely debated topic is the duration of bisphosphonate therapy. Due to the long duration of action of bisphosphonates and their effect on bone matrix, which can increase the risk of atypical fractures, many clinicians favor intermittent treatment and follow-up for any changes in bone mineralization [2].

Growth hormone has anabolic effects on the bone. Patients with OI do not have a growth hormone deficiency, but the use of growth hormone has been known to increase growth velocity and increase bone mineral density when used as a single drug therapy or in combination with a bisphosphonate [18, 19]. Denosumab, a monoclonal antibody to receptor activator of nuclear kappa B ligand, increased bone density and decreases bone resorption. Denosumab has been found to increase BMD and mobility in 4 children with type IV OI [20]. In addition, use of antibodies to sclerostin and Dickkopf-1 has been investigated due to their role in increasing osteoblastic activity through inhibition of WNT pathway [21].

Gene Therapy

The goal of gene therapy in OI is to neutralize the expression of the mutant allele at the molecular level. This can be primarily achieved by various methods. Transforming OI type II, III, or IV into type I by suppressing mutant allele to a null allele, enabling half the production of normal collagen using hammerhead ribozymes has been tried [22]. Gene silencing, targeted gene therapy, and specific vector therapy involving COL1A1 and COL1A2 genes are other novel methods that have been investigated.

References

1. Forlino A, Marini JC. Osteogenesis imperfecta. Lancet. 2016;387(10028):1657–71.
2. Marini J, Smith SM. Osteogenesis imperfecta. In: Feingold KR, Anawalt B, Boyce A, et al., editors. Endotext. South Dartmouth (MA): MDText.com, Inc. p. 2000. https://www.ncbi.nlm.nih.gov/books/NBK279109/.
3. Shaker JL, Albert C, Fritz J, Harris G. Recent developments in osteogenesis imperfecta. F1000Res. 2015;4:681. https://doi.org/10.12688/f1000research.6398.1. eCollection 2015.

4. Cabral WA, Chang W, Barnes AM, Weis M, Scott MA, Leikin S, et al. Prolyl 3-hydroxylase 1 deficiency causes a recessive metabolic bone disorder resembling lethal/severe osteogenesis imperfecta. Nat Genet. 2007;39(3):359–65.
5. Sillence D, Senn A, Danks DM. Genetic heterogeneity in osteogenesis imperfecta. J Med Genet. 1979;16(2):101–16.
6. Alharbi SA. A systematic overview of osteogenesis imperfecta. Mol Biol. 2016;5(1):1–9.
7. Byers PH, Krakow D, Nunes ME, Pepin M. Genetic evaluation of suspected osteogenesis imperfecta (OI). Genet Med. 2006;8(6):383.
8. Obafemi AA, Bulas DI, Troendle J, Marini JC. Popcorn calcification in osteogenesis imperfecta: incidence, progression, and molecular correlation. Am J Med Genet Part A. 2008;146(21):2725–32.
9. Thompson EM. Non-invasive prenatal diagnosis of osteogenesis imperfecta. Am J Med Genet. 1993;45(2):201–6.
10. Glorieux FH, Bishop NJ, Plotkin H, Chabot G, Lanoue G, Travers R. Cyclic administration of pamidronate in children with severe osteogenesis imperfecta. N Engl J Med. 1998;339(14):947–52.
11. Rauch F, Glorieux FH. Bisphosphonate treatment in osteogenesis imperfecta: which drug, for whom, for how long? Ann Med. 2005;37(4):295–302.
12. National Institute of Health: Osteoporosis and related bone diseases. Osteogenesis imperfecta overview. 2012. www.bones.nih.gov.
13. Yilmaz G, Hwang S, Oto M, Kruse R, Rogers KJ, Bober MB, Cahill PJ, Shah SA. Surgical treatment of scoliosis in osteogenesis imperfecta with cement-augmented pedicle screw instrumentation. Clin Spine Surgery. 2014;27(3):174–80.
14. Salehpour S, Tavakkoli S. Cyclic pamidronate therapy in children with osteogenesis imperfecta. J Pediatr Endocrinol Metab. 2010;23(1–2):73–80.
15. Vallo A, Rodriguez-Leyva F, Rodríguez Soriano J. Osteogenesis imperfecta: anthropometric, skeletal and mineral metabolic effects of long-term intravenous pamidronate therapy. Acta Paediatr. 2006;95(3):332–9.
16. Adami S, Gatti D, Colapietro F, Fracassi E, Braga V, Rossini M, Tato L. Intravenous neridronate in adults with osteogenesis imperfecta. J Bone Miner Res. 2003;18(1):126–30.
17. Gatti D, Rossini M, Viapiana O, Idolazzi L, Adami S. Clinical development of neridronate: potential for new applications. Ther Clin Risk Manag. 2013;9:139–47.
18. Antoniazzi F, Bertoldo F, Mottes M, Valli M, Sirpresi S, Zamboni G, et al. Growth hormone treatment in osteogenesis imperfecta with quantitative defect of type I collagen synthesis. J Pediatr. 1996;129(3):432–9.
19. Antoniazzi F, Monti E, Venturi G, Franceschi R, Doro F, Gatti D, et al. GH in combination with bisphosphonate treatment in osteogenesis imperfecta. Eur J Endocrinol. 2010;163(3):479–87.
20. Hoyer-Kuhn H, Netzer C, Koerber F, Schoenau E, Semler O. Two years' experience with denosumab for children with osteogenesis imperfecta type VI. Orphanet J Rare Dis. 2014;9(1):145.
21. Ke HZ, Richards WG, Li X, Ominsky MS. Sclerostin and Dickkopf-1 as therapeutic targets in bone diseases. Endocr Rev. 2012;33(5):747–83.
22. Dawson PA, Marini JC. Hammerhead ribozymes selectively suppress mutant type I collagen mRNA in osteogenesis imperfecta fibroblasts. Nucleic Acids Res. 2000;28(20):4013–20.

Chapter 39
Diabetes in Pregnancy

Melanie Baskind, Linda A. DiMeglio, and Michael D. Cabana

Abbreviations

ACOG	American College of Obstetricians and Gynecologists
CRS	Caudal regression syndrome
IDM	Infant(s) of diabetic mothers
SA	Sacral agenesis
USPSTF	United States Preventative Services Task Force

Elevated maternal blood glucose during pregnancy is a risk factor for both pre- and postnatal maternal and child complications. In general, the degree of these complications is proportional to overall glycemic control. One large-scale study showed this linear relationship was true even in women with blood glucose concentrations below those diagnostic of diabetes [1]. Infants of diabetic mothers (IDMs) are at

M. Baskind (✉)
Department of Pediatrics, UCSF Benioff Children's Hospital, San Francisco, CA, USA
e-mail: melanie.baskind@ucsf.edu

L. A. DiMeglio
Department of Pediatrics, Indiana University School of Medicine, Riley Hospital for Children, Indianapolis, IN, USA
e-mail: dimeglio@iu.edu

M. D. Cabana
Department of Pediatrics, Albert Einstein College of Medicine, Physician-in-Chief, The Children's Hospital at Montefiore (CHAM), Bronx, NY, USA
e-mail: mcabana@montefiore.org

J. F. Sarwark, R. L. Carl (eds.), *Orthopaedics for the Newborn and Young Child*,
https://doi.org/10.1007/978-3-031-11136-5_39

Table 39.1 Complications of infants of diabetic mothers

Early gestation
Miscarriage
Congenital malformations (e.g., caudal regression syndrome)
Cardiomyopathy
Late gestation
Stillbirth
Prematurity
Macrosomia
Perinatal asphyxia
Metabolic abnormalities
Hypoglycemia
Hypocalcemia
Hypomagnesemia
Low iron stores
Polycythemia and hyperviscosity
Hyperbilirubinemia
Respiratory distress syndrome

risk for a large number of complications at various points throughout gestation (Table 39.1). Orthopedic complications also may occur. Most commonly, these include clavicular fractures and brachial plexus injuries due to macrosomia and/or shoulder dystocia at the time of delivery. Caudal regression syndrome (CRS) is a less common but more severe complication. CRS is a spectrum of caudal anatomy agenesis, with manifestations that may include sacral agenesis (SA), kyphosis, scoliosis, hip and knee dislocations, flexion contractures, femoral hypoplasia, and foot anomalies.

Background

Hyperglycemia during pregnancy is a common phenomenon. In 2017 alone, there were 21.3 million (16.2%) live births with some form of hyperglycemia in pregnancy [2]. Hyperglycemia during pregnancy can occur either because of pregestational or gestational diabetes, the latter of which is defined by the American Diabetes Association as “diabetes diagnosed during the second or third pregnancy that was not clearly overt diabetes prior to pregnancy” [3]. About 85% of hyperglycemic pregnancies are due to gestational diabetes [2]. Pregestational diabetes is proportionally less common, but the risk of fetal exposure to high glucose concentrations at critical periods of development makes these pregnancies particularly high risk. As the number of diabetic women in the world continues to rise, from an estimated 204 million in 2017 to a projected 308 million by 2045 [2], so, too, will the incidence of IDMs.

The increasing incidence of IDMs is concerning because of the heightened risk of adverse birth outcomes, which range in severity from macrosomia to severe congenital anomalies. In one study from Ontario, Canada, the odds ratio of having a heart defect was 2.6 times higher in IDMs compared to infants born to non-diabetic mothers, and for neural tube defects 1.9 times higher [4]. CRS is rare, affecting only 0.1–0.25 per 10,000 pregnancies [5]. However, the likelihood of being diagnosed with CRS is more than 250 times higher in IDMs than in non-diabetic pregnancies [6].

To a certain extent, higher blood glucose concentrations during pregnancy are a physiologic phenomenon. In order to meet the increasing metabolic demands of a growing fetus, pregnant women increase their hepatic glucose production by 30% and placental hormones increase tissue insulin resistance [7]. Physiologically, this insulin resistance of pregnancy is transient, but gestational diabetes is associated with an elevated risk of being diagnosed with type 2 diabetes later in life, and children of mothers with gestational diabetes also have a higher risk of obesity and type 2 diabetes later in life.

The reasons for higher maternal blood glucose concentrations increasing the likelihood of fetal anomalies are multiple and not entirely elucidated. It is well-established that when maternal plasma glucose concentrations are high, glucose transporter proteins (GLUT) on placental syncytiotrophoblasts carry excess glucose to the fetus. This facilitative transport is mediated by concentration gradients, resulting in fetal hyperglycemia and hyperinsulinemia [7]. This fetal hyperglycemia and hyperinsulinemia, by mechanisms not clearly delineated, have a number of downstream effects. These include increased oxygen consumption and fetal hypoxemia thought to result in a range of metabolic and anatomic derangements, as well as excessive growth of insulin-sensitive tissues putting IDMs at risk of macrosomia [8]. Hyperglycemia during organogenesis (5–8 weeks after the last menstrual period) has been linked to alternations in gene expression in animal studies and is thought to play a critical role in intrauterine fetal demise and abnormal development seen in IDMs [7]. The pathophysiology leading to CRS has been shown to occur in the embryo before the fourth week of gestation and has been linked to a defect in the induction of the caudal elements at the mid-posterior axis of the mesoderm [9]. High glucose concentrations are one cause of this defect, but the fact that CRS occurs in pregnancies of non-diabetic mothers indicates there are other teratogens leading to the same outcome.

Clinical Presentation of Orthopedic Manifestations: History and Physical

History

When evaluating a known IDM who is presenting with orthopedic complications, providers should take a detailed history of the infant's prenatal, intrapartum, and postpartum course. In evaluating an infant with concern for clavicular fracture or

brachial plexus injury, providers should inquire about the difficulty of the delivery. For example, was there a shoulder dystocia? If so, for how long? After the delivery, did the baby move his or her arms symmetrically? Could the baby actively move both arms above the head?

In infants with congenital abnormalities of unknown etiology, it should be determined if the mother had a diagnosis of maternal diabetes either prior to or during the pregnancy, and how that diagnosis was established. What was the level of glycemic control during the pregnancy? Did the mother routinely monitor blood glucose concentrations at home? Was dietary intervention or insulin required? If prenatal ultrasounds were performed, were there any concerns for anatomic malformations, particularly in the second trimester anatomy screen? What was the birthweight? If the mother did not receive routine prenatal care, clues that the infant may have been exposed to high glucose concentrations during pregnancy may include specific complications such as macrosomia, fetal hypoglycemia, polycythemia, and hyperbilirubinemia.

Physical

The physical examination evaluating an IDM for orthopedic complications should evaluate for signs of clavicular fracture and brachial plexus injury. These topics are discussed in more detail in Chaps. 21 and 22. Briefly, these findings may include edema of the affected area, asymmetrical bone contour, decreased extremity movement, crying with limb manipulation or palpation, and an asymmetric Moro reflex. In the case of clavicular fracture, crepitus may be noted near the area of injury. Children with a brachial plexus injury may have characteristic arm resting positions, such as adduction and internal rotation of the arm and forearm extension (i.e., injury to C5-C6 or Erb palsy), or isolated hand paralysis and Horner syndrome (i.e., injury to C8-T1 or Klumpke palsy).

Congenital abnormalities may be obvious on physical exam, depending on the degree of severity. CRS is a spectrum of agenesis ranging from isolated anal atresia to complete absence of sacral, lumbar, and thoracic vertebrae. The most apparent anatomical abnormalities of CRS include an absent sacrum causing flattened and dimpled buttocks, ptergia of the popliteal region (i.e., “popliteal webbing”), flexion and abduction of the hips (i.e., “frog-leg” position), and a small pelvis with spinopelvic instability. By palpation and range of motion evaluation, one can assess whether or not there is femoral hypoplasia, and a thorough evaluation of the back and feet can assess the presence or absence of scoliosis, talipes equinovarus, calcaneovalgus deformities, and flexion contractures. Importantly, CRS can either be isolated to lower vertebral and extremity anomalies, or found in tandem with gastrointestinal, genitourinary, central nervous system, cardiac, and facial cleft defects. If an IDM presents with any of the above presents, CRS should be on the differential.

Evaluation of Orthopedic Manifestations

The most significant orthopedic manifestations of IDMs may be diagnosed prenatally by ultrasound. Most major anatomical defects can be detected between 18 and 20 weeks by routine second trimester ultrasound performed to assess fetal anatomy. A shorter than expected crown-rump length may be an early indication of CRS. Mild forms of CRS may be difficult to diagnose prior to 20 weeks, due to incomplete ossification of the sacrum.

In the postnatal period, any concerns on physical exam should prompt further imaging to confirm a diagnosis. A work-up for suspected clavicular, or in rare cases humeral, fracture, should include full radiographs of the chest and upper extremities. Brachial plexus injury is most commonly a diagnosis made on a physical exam, with further work-up pursued if the diagnosis is in question or if there is no evidence of recovery within a few months.

In cases where there is an absence of prenatal care, after physical examination, imaging is a key component of the evaluation and confirmation of major congenital abnormalities related to IDMs. Radiographs of the spine and pelvis are good starting points in making a diagnosis of CRS, with ultrasound and cross-sectional imaging important for evaluation that will dictate management. These imaging modalities aid in understanding the degree of disability and extent of SA, kyphosis and scoliosis, hip and knee dislocations, and femoral hypoplasia.

In relation to the classification of CRS, the characterization of SA is most well-established. The most well-known classification system for SA was proposed by Renshaw in 1978 [10], whereby radiographs of the spine and pelvis were used to group patients into one of four groups related to the bony defects between the spine and sacrum (see Table 39.2).

In 2002, Guille et al. proposed an alternative to the Renshaw classification, which distinguished between the presence or absence of myelomeningocele, with the goal of better predicting ambulatory potential to guide surgical management [11] (Table 39.3).

A case study of 38 patients with SA compared these classification systems and found little concordance [12]. Ultimately the lack of consensus surrounding how to best characterize SA may not be clinically significant, as approaches to treatment are multidisciplinary and individually tailored.

Table 39.2 Renshaw classification of Sacral Agenesis [10]. Adapted and reprinted from Renshaw TS, Sacral agenesis, Journal of Bone & Joint Surgery, Vol. 60/Issue 3, pages 373–383, © 1978, with permission from Wolters Kluwer Health, Inc.

I	Total or partial unilateral sacral agenesis
II	Partial sacral agenesis with a partial but bilaterally symmetrical defect and a stable articulation between the ilia and a normal or hypoplastic first sacral vertebra
III	Variable lumbar and total sacral agenesis with the ilia articulating with the sides of the lowest vertebra present
IV	Variable lumbar and total sacral agenesis, the caudal end-plate of the lowest vertebra resting above either fused ilia or an iliac amphiarthrosis

Table 39.3 Guille classification of sacral agenesis [11]. Adapted and reprinted from Guille JT, Benevides R, DeAlba CC, Siriram V, Kumar SJ, Lumbosacral agenesis: a new classification correlating spinal deformity and ambulatory potential, Journal of Bone & Joint Surgery, Vol. 84/ Issue 1, pages 32–38, © 2002, with permission from Wolters Kluwer Health, Inc.

Group I	Absence of myelomeningocele
Group II	Presence of myelomeningocele
	Type A: Slight gap between the ilia or the ilia were fused in the midline. One or more lumbar vertebrae were absent. The caudad aspect of the spine is articulated with the pelvis in the midline, maintaining its vertical alignment
	Type B: Ilia were fused together, some of the lumbar vertebrae were absent, and the most caudal lumbar vertebra articulated with one of the ilia, with the most caudad aspect of the spine shifted away from the midline
	Type C: Total agenesis of the lumbar spine, ilia fused together, visible gap between the most caudad intact thoracic vertebra and pelvis

Treatment/Management of Orthopedic Manifestations

The majority of clavicular fractures and brachial plexus injuries resolve on their own with excellent prognoses. Mainstays of clavicular fracture management include acetaminophen (i.e., paracetamol, N-acetyl-p-amino-phenol, or APAP) for pain, careful handling, and parental reassurance. Parents can use a garment to pin the affected arm to the chest, keeping the elbow at 90°. Radiographs should be repeated to confirm proper healing.

The management of brachial plexus injury is slightly more controversial. In cases of severe nerve injury, most providers will refer to physical therapy and only move towards surgical intervention if recovery is not complete after 3 or more months. Physical therapy aims to prevent contractures, provides supportive splints, and works on muscle strengthening exercises. If necessary, surgical interventions include nerve transfers from donors and shoulder reconstruction to correct internal rotation.

CRS primary pathology is irreversible and treatment is supportive. Due to the multiple organ systems that can be involved, and high degree of variability in presentation, each case requires an individual approach with a multidisciplinary treatment team. Aside from orthopedic surgery, these groups often involve genitourinary and neuromuscular expertise. Ultimately, management is tailored to and dependent on the child's degree of dysfunction with the goal of maximizing functionality. This goal is achieved by reducing any contractures, addressing hip and knee dislocations, and fitting braces for foot abnormalities. Renshaw classification type I and II are typically nonoperative approaches, making use of physical therapy and braces, while type III and IV are more severe deformities often requiring multiple surgeries. In these patients, surgery is used for spinal stabilization procedures and limb amputation for nonfunctional lower limb deformities with the purpose of improving mobility. Severe kyphosis and scoliosis are corrected, and the pelvis is stabilized via metal implant with spinopelvic fusion to allow for sitting and/or standing.

Clinical Vignette

A newborn girl is born at 38 weeks to a G5P4 mother with limited prenatal care. The baby's mother reported significant substance use, including alcohol, marijuana, and tobacco for 6 months of pregnancy, prior to her realizing she was pregnant. There was no glucose tolerance test on record. The baby had an uncomplicated vaginal delivery with Apgars of 8 (1 min) and 9 (5 min) but was found on exam to have lower extremity anomalies, prompting transfer of care to a tertiary care center.

Physical exam was notable for an anteriorly malpositioned anus with mucosal connection to the vagina, a bony prominence of the lumbar spine with an abnormal or absent sacrum, a dimple of the lateral buttocks, bilateral legs malpositioned with knees in extension, atrophic lower extremities distal to the knee with no spontaneous movement, and an inverted left foot. CRS was confirmed by a radiograph of the abdomen and pelvis that showed absence of the sacrum and lower lumbar spine. Spinal ultrasound showed dysgenesis of the distal lumbar spine, conus medularis terminating at T12, and clumped/hypomobile nerve roots. An ultrasound of the hips showed developmental dysplasia of both hips with bilateral dislocation.

Inpatient consults included orthopedics, urology, pediatric surgery, neurology, neurosurgery, genetics and rehabilitation, and early management included intermittent catheterization and anal dilation followed by diverting sigmoid colostomy for urinary and stool incontinence. Once stable for discharge, the infant will require follow-up in a multidisciplinary clinic that includes rehabilitation, urology, neurosurgery, and orthopedics. Pediatric orthopedic clinical care will address needs related to hip flexion and knee extension contractures. Management issues to consider include clubfoot Ponseti casting, a Pavlik harness, and other surgical interventions as needed.

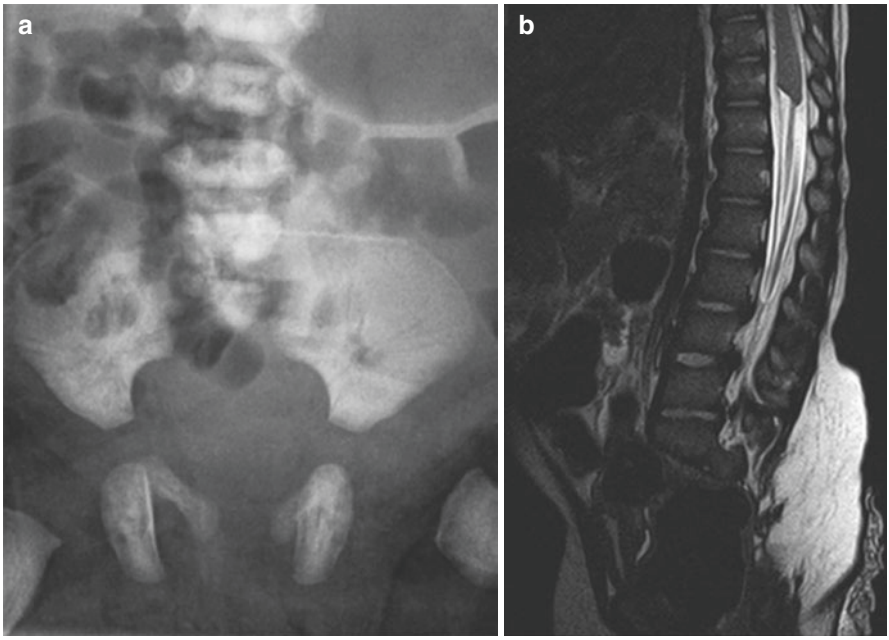
Natural History, Primary, and Secondary Prevention

Elevated maternal blood glucose concentrations that go undiagnosed and unchecked during pregnancy expose the fetus to high concentrations of glucose and insulin while in utero, putting them at high risk for complications ranging from macrosomia to early fetal demise. Primary prevention of infant complications from maternal diabetes involves tight glycemic control throughout pregnancy. This control requires early diagnosis of gestational diabetes, timely pregnancy recognition and appropriate therapy for women with known diabetes, and early recognition of previously undiagnosed pregestational diabetes.

The US Preventative Services Task Force (USPSTF), based on level B grade evidence, recommends screening for gestational diabetes in asymptomatic pregnant women after 24 weeks gestation [13]. The American College of Obstetricians and Gynecologists (ACOG) recommends screening for gestational diabetes between 24 and 28 weeks of gestation, and screening for pregestational diabetes earlier in

pregnancy if risk factors are present [14, 15]. When this diagnosis is established, regular blood glucose monitoring should be done to titrate treatment appropriately. In terms of secondary prevention, per ACOG, women with pregestational diabetes without other comorbidities or complications should deliver between 39 0/7 weeks and 39 6/7 weeks [15]. If the estimated fetal weight is 4500 grams or greater, cesarean delivery should be considered to prevent birth injuries [15]. With regard to congenital abnormalities associated with diabetes during pregnancy, early recognition of any defects, ideally during the second trimester of pregnancy, will prompt earlier intervention to maximize functionality.

Pelvic radiograph and spinal MRI of a female with caudal regression syndrome, at **(a)** 5 days and **(b)** 2 years of life, respectively. Both images show an absent distant sacrum and coccyx, with the MRI showing a truncated appearance of the spinal cord terminating at T11–T12. Figures courtesy of Megan Marine, MD, Indiana University School of Medicine, Department of Radiology



References

1. HAPO Study Cooperative Research Group. Hyperglycemia and adverse pregnancy outcomes. N Engl J Med. 2008;358(19):1991–2002.
2. IDF: International Diabetes Federation. IDF Diabetes Atlas, 8th edn. Brussels, Belgium: International Diabetes Federation; 2017. https://www.idf.org/our-activities/care-prevention/gdm. Accessed 29 Nov 2018.
3. American Diabetes Association. 2. Classification and diagnosis of diabetes: standards of medical care in diabetes—2019. Diabetes Care. 2019;42(Supplement 1):S13–28.

4. Agha MM, Glazier RH, Moineddin R, Booth G. Congenital abnormalities in newborns of women with pregestational diabetes: a time-trend analysis, 1994 to 2009. Birth Defects Res A Clin Mol Teratol. 2016;106:831–9. (Level II-3).
5. Cullier F, Charpentier AS, M'Lamali H, Colbert R. Jarcho—Levin syndrome with caudal regression. http://www.thefetus.net. Accessed 15 Dec 2005.
6. Mills JL. Malformations in infants of diabetic mothers. Teratology. 1982;25:385.
7. Reddy Kallem V, Pandita A, Pillai A. Infant of diabetic mother: what one needs to know? J Matern Fetal Neonatal Med. 2018:1–11. https://doi.org/10.1080/14767058.2018.1494710. [Epub ahead of print].
8. Philipps AF, Dubin JW, Matty PJ, Raye JR. Arterial hypoxemia and hyperinsulinemia in the chronically hyperglycemic fetal lamb. Pediatr Res. 1982;16(8):653.
9. Boulas MM. Recognition of caudal regression syndrome. Adv Neonatal Care. 2009;9(2):61–9.
10. Renshaw TS. Sacral agenesis. J Bone Joint Surg Am. 1978;60(3):373–83.
11. Guille JT, Benevides R, DeAlba CC, Siriram V, Kumar SJ. Lumbosacral agenesis: a new classification correlating spinal deformity and ambulatory potential. JBJS. 2002;84(1):32–8.
12. Balioğlu MB, Akman YE, Ucpunar H, Albayrak A, Kargın D, Atıcı Y, Büyük AF. Sacral agenesis: evaluation of accompanying pathologies in 38 cases, with analysis of long-term outcomes. Childs Nerv Syst. 2016;32(9):1693–702.
13. U.S. Preventive Services Task Force. Gestational diabetes mellitus, screening. https://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/gestational-diabetes-mellitus-screening. Accessed 16 Jan 2019.
14. Committee on Practice Bulletins—Obstetrics. ACOG Practice Bulletin No. 190: gestational diabetes mellitus. Obstet Gynecol. 2018;131(2):e49–64.
15. Committee on Practice Bulletins—Obstetrics. ACOG Practice Bulletin No. 201: pregestational diabetes mellitus. Obstet Gynecol. 2018;132(6):E228–48.

Chapter 40
Down Syndrome

Mary E. Dubon, Andrea Paulson, and Priya Chandan

Background

Down syndrome is a chromosomal abnormality in which an individual has extra genetic material from Chromosome 21 present in their cells. This extra genetic material results in a variable phenotype; however, there are many commonly found features that assist in the diagnosis and include potential for malformations, cognitive impairment, and medical conditions [1]. All individuals suspected of having Down syndrome require diagnosis and appropriate screening for associated conditions.

M. E. Dubon (✉)
Department of Pediatric Rehabilitation, Spaulding Rehabilitation Hospital, Charlestown, MA, USA

Department of Orthopedic Surgery and Division of Sports Medicine, Boston Children's Hospital, Boston, MA, USA

Department of Physical Medicine & Rehabilitation, Harvard Medical School, Boston, MA, USA
e-mail: mary.dubon@childrens.harvard.edu

A. Paulson
Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, OH, USA
e-mail: andrea.paulson@Cchmc.org

P. Chandan
Division of Physical Medicine & Rehabilitation, University of Louisville, Louisville, KY, USA
e-mail: priya.chandan@louisville.edu

J. F. Sarwark, R. L. Carl (eds.), *Orthopaedics for the Newborn and Young Child*,
https://doi.org/10.1007/978-3-031-11136-5_40

Epidemiology and Pathophysiology

Down syndrome is the most common inherited genetic syndrome. It is named after John Langdon Down who first described the syndrome in 1866 [2]. According to the Centers for Disease Control and Prevention approximately 1 in every 700 babies born in the United States is born with Down syndrome or approximately 6000 babies annually. Factors that are associated with an increased risk of having a child with Down syndrome include advanced maternal age, a previous child with a chromosomal abnormality, and a parental balanced translocation or other chromosomal disorder [3].

There are three separate mechanisms that can result in an individual having extra genetic material in their cells. There is a region of chromosome 21, 21q22.3, which is considered a critical region that results in the phenotype. The most common mechanism, which accounts for 95% of children with Down syndrome, is considered a nonfamilial trisomy 21. This occurs due to sporadic complete nondisjunction during cell meiosis and results in a gamete with 47 chromosomes, including an extra chromosome 21, which is present in all cells in the body. In approximately 4% of individuals with Down syndrome, the extra genetic material is the result of an unbalanced translocation between chromosome 21 and another chromosome. The majority of translocations are de novo, but approximately one-quarter are related to familial translocations. In approximately 1% of cases, an individual will have two different cell lines present, one of which has trisomy 21 and the other is genetically normal. This is called mosaicism. In individuals with mosaic Down syndrome, the phenotype is typically milder; however, there is still a risk of all of the associated medical comorbidities associated with Down syndrome, warranting appropriate screening. Genetic counseling should be provided for individuals and families [1].

Common Clinical Presentation

Down syndrome is often detected during prenatal screening followed by diagnostic testing if the screening results warrant further investigation; however, in some cases, it is detected following birth due to clinical features. The most common clinical exam findings in newborns are described in Table 40.1 [1].

Table 40.1 Common clinical findings in newborns with Down syndrome [1]

Organ system	Clinical finding
HEENT	Small mouth, small ears, increased or excessive skin at the posterior neck, a small brachycephalic head, flat nasal bridge, upward-slanting palpebral fissures, epicanthal folds, brushfield spots
Cardiovascular	Cardiac murmur, cyanosis, or hemodynamic instability
Respiratory	Difficulty breathing
Gastrointestinal	Duodenal atresia, Hirschsprung disease, poor feeding, imperforate anus
Musculoskeletal	Single transverse palmar crease, short fifth finger with clinodactyly, deep plantar groove between the first and second toes, hip dysplasia
Neurological	Poor moro reflex, hypotonia
Skin	Cutis marmorata, hyperkeratosis

Genetic Testing

It is important to determine the location of the additional genetic material in Down syndrome as this can affect genetic counseling for the child and their parents. Chromosomes can be assessed by karyotype with microarray or florescent in situ hybridization (FISH) testing, which can be completed during pregnancy or following delivery. Testing during pregnancy requires a chorionic villus sample (material from the placenta), an amniocentesis (amniotic fluid), or a percutaneous umbilical blood sampling (blood from the umbilical cord). Following delivery, whole blood from the child can be sent for analysis if there is concern on the physical exam [1].

Management

Once a child has been diagnosed with Down syndrome, or is suspected of having Down syndrome, the commonly associated conditions need to be screened for and managed and proper anticipatory guidance should be provided. Commonly associated conditions that the clinician should be aware of include the following, separated by body system [1, 2]:

- **Cognitive**: Intelligence quotient varies from mild to severe. Global developmental delay is common and early intervention therapy services for fine motor, gross motor, and cognitive skills are important. There is an **increased** risk of early onset dementia.
- **HEENT**: Congenital hearing loss must be screened for at birth by objective testing such as brainstem auditory evoked response or otoacoustic emission and following up assessment within 3 months. Congenital cataracts need to be assessed for by looking for a red reflex. If detected, congenital cataracts require prompt evaluation and treatment by an Ophthalmologist. Severe refractive errors are also common and all children with Down syndrome require routine vision screening.
- **Cardiovascular**: Congenital heart defects are present in approximately 50% of individuals with Down syndrome and all children require an echocardiogram following delivery. Common abnormalities include ventricular septal defect, endocardial cushion defect, atrial septal defect, aberrant subclavian artery, mitral valve prolapse, tricuspid valve prolapse, or aortic regurgitation.
- **Respiratory**: Hypotonia can result in respiratory concerns, necessitating respiratory screening. Stridor, wheezing, or noisy breathing may be observed and require further assessment for airway anomalies by a Pulmonologist for conditions, as pulmonary conditions such as sleep apnea can occur in this population. If not properly treated, sleep apnea can affect cognition and behavior.
- **Gastrointestinal:** Hypotonia, as seen in Down syndrome, can result in poor feeding with choking and aspiration. Children with Down syndrome are also at a higher risk of failure to thrive, duodenal atresia, and/or duodenal stenosis. Constipation is common and can be secondary to restricted diet, hypotonia, hypothyroidism, Hirschsprung disease, gastrointestinal tract malformation, or

stenosis. Gastroesophageal reflux can also result in failure to thrive or respiratory concerns if severe.

- **Hematology**: Leukemoid reactions or transient myeloproliferative disorder (TMD) is present in nearly 10% of newborns with Down syndrome and is assessed by obtaining a complete blood count. TMD usually improves in the first 3 months; however, children with Down syndrome are at higher risk for later onset leukemia. Polycythemia is also common and requires careful management.
- **Endocrine**: Congenital hypothyroidism is present in 1% of children with Down syndrome and screening with both TSH and free T4 is required. Hypothyroidism should be screened for in this population and if not treated can worsen developmental delay.
- **Musculoskeletal**: Down syndrome is also associated with orthopedic manifestations, as described in the following section.

Orthopedic Conditions Associated with Down Syndrome

General Considerations

Hypotonia, or low muscle tone, is commonly seen in Down syndrome. This is easily assessed on physical examination by passive range of motion, noting decreased resistance compared to children with normal muscle tone. The presence of hypotonia can predispose to orthopedic comorbidities, as discussed further in the following sections.

Ligamentous laxity is another common finding in Down syndrome. On clinical examination, ligamentous laxity presents with joint hypermobility. This can result in hip instability, patellar instability, pes planus, cervical spine instability, and/or atlantoaxial instability [4]. In adults, scales such as the Beighton Score (which scores hypermobility based on the ability to touch the floor with one's palms with forward lumbar flexion, passively extend the fifth digit past 90°, passively abducting the thumb to touch the forearm with the wrist flexed, passively extend the elbows to 10° past neutral, and passively extend the knees to 10° past neutral) can be used to quantify hypermobility [5]. This scale has not been validated in the pediatric population; however, similar maneuvers are often used to assess joint hypermobility. It is important to note that in the general pediatric population, hypermobility and joint laxity at appendicular joints seen in childhood do not necessarily proceed into adulthood, which adds another challenge to deciphering pathologic versus non-pathologic ligamentous laxity in the pediatric population [6]. Ligamentous laxity is thought to be a common reason for other orthopedic comorbidities in Down syndrome.

Likely multifactorial, individuals with Trisomy 21 often have delays in motor milestones and delayed onset of ambulation, ambulating on average 1 year after the general population; however, ambulating is typically achieved [4]. This highlights the importance of screening children with Down syndrome for the achievement of

developmental milestones and referring children with Down syndrome who have hypotonia, weakness, cognitive delays, and/or developmental delays to early intervention services to work on gross motor, fine motor, and cognitive skills for development.

Atlantoaxial Instability and Occipitocervical Instability

Patients with Down syndrome are at increased risk of atlantoaxial instability (AAI), which refers to increased movement between the first and second cervical vertebrae at the atlantoaxial joint. While the prevalence of AAI ranges from 7 to 27% in individuals with Down syndrome, less than 1–2% of patients develop symptomatic AAI [7]. The overarching concern is that excessive movement at the atlantoaxial joint can lead to neurologic injury if the spinal cord becomes impinged [7]. Thus, clinical guidelines focus on minimizing the risk of neurologic injury through positioning and monitoring neurologic symptoms over time, as changes in symptoms raise concern for neurologic impingement and/or damage.

The American Academy of Pediatrics 2011 Clinical Report—Health Supervision for Children with Down syndrome discusses clinical considerations in the management of AAI in children with Down syndrome. Parents should be advised, at least biennially, of the importance of cervical spine-positioning precautions during anesthetic, surgical, or radiographic procedures. Parents should also be counseled to contact their physician for new onset of changes in gait, changes in the use of arms or hands, changes in bowel or bladder function, neck pain, stiff neck, head tilt, torticollis, change in how the child positions his or her head, change in general function, spasticity, or weakness. Of note, spasticity is a sign of central nervous system disease and can present as a normal tone in a child with hypotonia. Myelopathic signs and symptoms should be evaluated at every well-child visit or when symptoms, as described above, are reported by parents. Of note, routine radiologic evaluation of the cervical spine in asymptomatic children is not recommended. Plain cervical spine radiography in the neutral position is indicated only if the child is symptomatic, as described above. If these images show radiographic abnormalities, the child should be referred as quickly as possible to a pediatric neurosurgeon or pediatric orthopedic surgeon with expertise in evaluating and treating AAI. If no significant radiographic abnormalities are present, flexion and extension radiographs may be obtained before the patient is promptly referred for surgical evaluation/treatment [1].

There are also considerations regarding sports participation by children with Down syndrome. The American Academy of Pediatrics recommends advising parents that participation in some sports, including contact sports such as football, soccer, and gymnastics (usually at older ages) places children at increased risk of spinal cord injury. Additionally, trampoline use by all children younger than 6 years should be avoided, while older children should have direct professional supervision

[1]. Special Olympics International (SOI)'s current policy on AAI screens for symptoms concerning for spinal cord compression during the preparticipation physical examination (PPE), but no longer requires radiographs as a prerequisite for participation [8]. The provider completing the PPE indicates the presence or absence of neurologic symptoms and/or neurologic physical exam findings associated with spinal cord compression. If symptoms and/or physical exam findings are present, the athlete must undergo additional neurological evaluation to determine medical clearance and the athlete/guardian must sign the "Special Release Concerning Spinal Cord Compression and/or Symptomatic Atlantoaxial Instability," acknowledging they have been informed of the findings and physician recommendations [9]. Thus, both the American Academy of Pediatrics and Special Olympics International base sports participation for patients with increased risk of AAI, such as patients with Down syndrome, off of the preparticipation history and physical exam, rather than on radiographic evaluation.

In addition to AAI, occipitocervical instability (OCI), or instability at the occiput to C1 junction, is also a consideration in patients with Down syndrome. Given that OCI is difficult to assess on plain radiographs due to bony overlap of the structures at the base of the skull, symptomatic patients may need a dynamic flexion-extension cervical spine MRI scan under supervision in order to evaluate cord compression [10].

Hip Instability and Other Hip Conditions

Although there are structural characteristics of the hip in Down syndrome that would lend toward more structural stability of the hip, including a deep, horizontal acetabulum, with decreased acetabular anteversion and increased femoral anteversion, there is actually a 1–7% prevalence of hip instability (tendency for hip subluxation or dislocation) in Down syndrome. This is thought to be secondary to the predisposition to increased laxity in this population and the tendency toward sitting in hip external rotation, which is commonly seen in Down syndrome, likely due to hypotonia [4, 11, 12]. Hip subluxations or dislocations can present with pain or gait abnormalities/limping. Hip instability can be treated in some cases with conservative strategies, such as closed reduction and immobilization of hip dislocations, or may require surgical correction [4]. Certainly, acute hip dislocations require immediate emergency management for relocation to avoid complications, such as avascular necrosis, from delayed relocation [13]. Referral to Orthopedics for evaluation and management of a child with suspected hip instability is important for the appropriate management and for the prevention of complications at the hip, such as acetabular dysplasia, hip degeneration changes, pain, and functional impairments in adulthood [4, 14].

Other hip conditions have been reported with increased incidence in Down syndrome, including slipped capital femoral epiphysis (SCFE), Perthes disease,

avascular necrosis, and osteoarthritis; therefore, it is important to screen for hip symptoms in this population and to arrange for appropriate care and referrals when symptoms arise [10, 15–17].

Patellofemoral Instability

Patellofemoral instability is the most common condition of the knee in individuals with Down syndrome [18]. This describes increased movement of the patella that in some cases can lead to dislocation [18]. Its prevalence in Down syndrome is thought to be 5–20%, with this relatively high prevalence thought to be due to the increased joint laxity often seen in Down syndrome [4, 18, 19]. Patellofemoral instability can be asymptomatic or can present with pain, falls, gait anomalies, or frank dislocation [18, 20]. It is typically treated conservatively with physical therapy and consideration of bracing; however, in some instances, particularly with recurrent frank dislocations, surgery is recommended [4, 18, 20]. Individuals with symptomatic patellofemoral instability should therefore be referred for orthopedic evaluation for physical therapy, bracing, or, in some instances, surgery.

Scoliosis

The prevalence of scoliosis in Down syndrome is thought to be around 10%; however, a recent study corrected for age by eliminating individuals less than 8 years old from the study sample and revealed a prevalence of 21% [21, 22]. The median age of onset is 14 years old (range 8–20 years old) [21]. There is also thought to be an increased risk of developing scoliosis in children who have undergone cardiothoracic surgery [22, 23]. This highlights the importance of screening for scoliosis in all children with Down syndrome, with special attention to those who have undergone cardiothoracic surgery [21, 22]. Referral to Orthopedics should be made for individuals with scoliosis for ongoing evaluation and management with observation, bracing, or surgery, dependent on the severity of the curvature.

Arthropathy of Down Syndrome

Arthropathy of Down syndrome is a rare condition affecting approximately 1% of individuals with Down syndrome [4]. Just like hypothyroidism, celiac disease, and diabetes mellitus, it is thought to be an autoimmune condition associated with Down syndrome. Arthropathy of Down syndrome however is unique in that it is an autoimmune condition specific to individuals with Down syndrome. It is considered a

unique entity from juvenile idiopathic arthritis (JIA) [24, 25]. It can be polyarticular or oligoarticular in nature at initial presentation; however, cases that are oligoarticular in nature often progress to become polyarticular in nature [24]. Arthropathy of Down syndrome can impact the cervical spine, metacarpophalangeal joints, hips, patellofemoral joints, and the ankles and can predispose individuals to joint subluxations, including, most concerningly, risk for cervical subluxation [4]. Recognition and treatment of this condition is important as proper medical management can help prevent permanent joint damage [24]. When evaluating joint range of motion restrictions, underlying hypermobility should be considered, as joint range of motion restrictions in an individual with baseline joint hypermobility may present with a neutral end range, for example [24, 25]. Referral to rheumatology is important for management and close follow-up of Arthropathy of Down syndrome [4]. See above for management of cervical subluxation.

Pes Planus

Pes planus, or flat feet, can be divided into flexible and rigid subtypes. Flexible pes planus is due to soft tissue structures and is not bony in nature, while rigid pes planus is secondary to bony causes, such as tarsal coalition [26]. Just as in the general population, in individuals with Down syndrome, flexible pes planus is more commonly seen than rigid pes planus. Flexible pes planus in Down syndrome is thought to be secondary to ligamentous laxity and hypotonia [4, 27–29]. Unless causing pain, falls, functional impairments, or other concerning symptoms, flexible pes planus in children does not require intervention. If causing symptoms, such as foot pain, knee pain, or functional impairments, treatment includes arch support with a shoe insert (in children, a full foot length shoe insert is recommended) or physical therapy for exercises such as intrinsic foot strengthening and/or Achilles tendon stretching. Surgical intervention is reserved for cases of symptomatic rigid pes planus [4].

Other Foot Conditions

Another foot condition associated with Down syndrome include metatarsus primus varus (an increased intermetatarsal angle between the first and second metatarsals), which can lead to secondary hallux valgus, or bunion, formation [28, 30]. These foot conditions can make finding appropriate shoe wear difficult, given the need for wide toe boxes [4]. In most cases, treatment is nonsurgical, through the use of wide-toe box shoes; however, in instances of pain or functional impairments secondary to these foot conditions, surgery can be considered [4]. The Special Olympics has an initiative called Fit Feet, which offers podiatric screenings for individuals with intellectual/developmental disabilities. Research from this initiative has suggested a high prevalence of podiatric conditions in individuals with intellectual/developmental disabilities, including the abovementioned conditions and others, such as fungal

infections (onychomycosis or tinea pedis) or onychocryptosis (ingrown toenails) [31]. This highlights the importance of screening foot examinations for this population and appropriate referral to Orthopedics or Podiatry when necessary.

Clinical Pearls

- Down syndrome is a chromosomal abnormality in which an individual has extra genetic material from Chromosome 21 present in their cells.
- Down syndrome is associated with systemic manifestations, including congenital heart disease, hypothyroidism, hematologic malignancies, sleep apnea, and Hirschsprung disease.
- Congenital cardiac disease is common and should be screened for in all children with Down syndrome.
- Hypothyroidism must be screened for and if not treated can worsen developmental delay.
- Hematological malignancies are more common in this population.
- Sleep apnea should be screened for and can affect cognition and behavior.
- Hypotonia and ligamentous laxity, commonly seen in Down syndrome, can lead to an increased risk of orthopedic complications.
- Orthopedic manifestations of Down syndrome include atlantoaxial instability, occipitocervical instability, patellofemoral instability, hip instability, pes planus, arthropathy of Down syndrome, and scoliosis.
- Screening for atlantoaxial instability is performed via comprehensive history and physical examination focused on evaluating for myelopathic signs, torticollis, or neck pain. Radiologic imaging is only performed in instances of suspected symptomatic atlantoaxial instability.
- Counseling about signs/symptoms of symptomatic atlantoaxial instability and positioning considerations for anesthetic, surgical, or radiographic procedures should be incorporated into patient and family education for individuals with Down syndrome.
- Spasticity is a sign of central nervous system disease and can present as a normal tone in a child with hypotonia.
- When evaluating joint range of motion restrictions, underlying hypermobility should be considered, as joint range of motion restrictions in an individual with baseline joint hypermobility may present with neutral end range, for example.

Conclusion

Down syndrome is a chromosomal abnormality in which an individual has extra genetic material from chromosome 21 present in their cells. There are cardiac, respiratory, neurologic, endocrine, gastrointestinal, and orthopedic manifestations. Congenital cardiac disease is common and should be screened for in all children

with Down syndrome. Orthopedic manifestations include patellofemoral instability, hip instability, arthropathy of Down syndrome, atlantoaxial instability, and occipitocervical instability.

References

1. Bull MJ. Health supervision for children with down syndrome. Pediatrics. 2011;128:393–406.
2. Ran Shin M, Trovato M. Down syndrome. PM&R Knowl Now. 2012. https://now.aapmr.org/down-syndrome/. Accessed 9 Nov 2018.
3. Parker SE, Mai CT, Canfield MA, et al. Updated national birth prevalence estimates for selected birth defects in the United States, 2004-2006. Birth Defects Res Part A Clin Mol Teratol. 2010;88:1008–16.
4. Caird MS, Wills BPD, Dormans JP. Down syndrome in children: the role of the orthopaedic surgeon. J Am Acad Orthop Surg. 2006;14:610–9.
5. Beighton PH, Grahame R, Bird H. Hypermobility of joints. London: Springer Nature; 2012.
6. Lamari NM, Chueire AG, Cordeiro JA. Analysis of joint mobility patterns among preschool children. Sao Paulo Med J. 2005;123:119–23.
7. Tomlinson C, Campbell A, Hurley A, Fenton E, Heron N. Sport preparticipation screening for asymptomatic atlantoaxial instability in patients with down syndrome. Clin J Sport Med. 2020;30(4):293–5. https://doi.org/10.1097/JSM.0000000000000642.
8. 2018 Special Olympics International Medical Form Instructions.
9. 2017 Special Olympics International. Article 1: Sports Rules.
10. Mik G, Gholve PA, Scher DM, Widmann RF, Green DW. Down syndrome: orthopedic issues. Curr Opin Pediatr. 2008;20:30–6.
11. Shaw ED, Beals RK. The hip joint in Down's syndrome. A study of its structure and associated disease. Clin Orthop Relat Res. 1992;(278):101–7.
12. Abousamra O, Bayhan IA, Rogers KJ, Miller F. Hip instability in down syndrome: a focus on acetabular retroversion. J Pediatr Orthop July/August. 2016;36(5):499–504.
13. Sulaiman AR, Munajat I, Mohd FE. Outcome of traumatic hip dislocation in children. J Pediatr Orthop B. 2013;22:557–62.
14. Kelley SP, Wedge JH. Management of hip instability in trisomy 21. J Pediatr Orthop. 2013;33:33–8.
15. Bosch P, Johnston CE, Karol L. Slipped capital femoral epiphysis in patients with Down syndrome. J Pediatr Orthop. 2004;24(3):271–7.
16. Dietz FR, Albanese SA, Katz DA, Dobbs MB, Salamon PB, Schoenecker PL, Sussman MD. Slipped capital femoral epiphysis in down syndrome. J Pediatr Orthop. 2004;24(5):508–13.
17. Hutchins KL. Slipped capital femoral epiphysis and hypothyroidism in a patient with Down syndrome. J Am Acad Physician Assist. 2013;26:35–7.
18. Duque Orozco MDP, Abousamra O, Chen BPJ, Rogers KJ, Sees JP, Miller F. Knee deformities in children with down syndrome: a focus on knee malalignment. J Pediatr Orthop. 2018;38:266–73.
19. Merrick J, Ezra E, Josef B, Hendel D, Steinberg DM, Wientroub S. Musculoskeletal problems in Down Syndrome European Paediatric Orthopaedic Society Survey: the Israeli sample. J Pediatr Orthop B. 2000;9:185–92.
20. Bettuzzi C, Lampasi M, Magnani M, Donzelli O. Surgical treatment of patellar dislocation in children with Down syndrome: a 3- to 11-year follow-up study. Knee Surgery, Sport Traumatol Arthrosc. 2009;17:334–40.
21. Abousamra O, Duque Orozco MP, Er MS, Rogers KJ, Sees JP, Miller F. Scoliosis in Down's syndrome. J Pediatr Orthop B. 2017;26:383–7.

22. Milbrandt TA, Johnston CE. Down syndrome and scoliosis: a review of a 50-year experience at one institution. Spine (Phila Pa 1976). 2005;30:2051–5.
23. Bal S, Elshershari H, Celiker R, Celiker A. Thoracic sequels after thoracotomies in children with congenital cardiac disease. Cardiol Young. 2003;13:264–7.
24. Juj H, Emery H. The arthropathy of down syndrome: an underdiagnosed and under-recognized condition. J Pediatr. 2009;154:234–8.
25. Olson JC, Bender JC, Levinson JE, Oestreich A, Lovell DJ. Arthropathy of Down syndrome. Pediatrics. 1990;86:931–6.
26. Carr Ii JB, Yang S, Lather LA. Pediatric pes planus: a state-of-the-art review. Pediatrics March 2016;137(3):e20151230.
27. Pau M, Galli M, Crivellini M, Albertini G. Foot–ground interaction during upright standing in children with Down syndrome. Res Dev Disabil. 2012;33:1881–7.
28. Concolino D, Pasquzzi A, Capalbo G, Sinopoli S, Strisciuglio P. Early detection of podiatric anomalies in children with Down syndrome. Acta Paediatr Int J Paediatr. 2006;95:17–20.
29. Galli M, Cimolin V, Rigoldi C, Pau M, Costici P, Albertini G. The effects of low arched feet on foot rotation during gait in children with down syndrome. J Intellect Disabil Res. 2014;58:758–64.
30. Staheli LT. Fundamentals of pediatric orthopedics. 5th ed. Seattle, WA: Wolters Kluwer; 2016.
31. Jenkins DW, Cooper K, Heigh EG. Prevalence of podiatric conditions seen in Special Olympics athletes: a comparison of USA data to an international population. Foot. 2015;25:5–11.

Chapter 41
Beckwith-Wiedemann Syndrome

Suzanne Amaro

Overview

Beckwith-Wiedemann syndrome (BWS) is a genetic disorder that predisposes children to pediatric cancers caused by changes in chromosome 11p15. The development of this chromosomal anomaly is believed to be caused by multi-locus imprinting disturbances, resulting in mis-expression of growth genes leading to the overgrowth that characterizes the condition. BWS is characterized by macrosomia, macroglossia, hemihyperplasia, visceromegaly with consequent abdominal wall defects, and increased risk of embryonal tumors such as Wilms' tumor, hepatoblastoma, neuroblastoma, and rhabdomyosarcoma [1]. About 15% of patients diagnosed with BWS have a familial link, and 85% is sporadic [2].

Epidemiology

The incidence of BWS is approximately 1 to every 26,000 births [3]. Children conceived by assisted reproductive technologies have been observed to have an increased risk for imprinting disorders, including BWS, but literature reports are inconsistent [3]. It is believed that the incidence of BWS in children conceived through assistive reproductive technology is about 1 in 1200 births [3]. Diagnosed patients have an increased risk of tumor development; therefore, periodic screening

S. Amaro (✉)
Department of Orthopaedic Surgery, Ann & Robert H. Lurie Children's Hospital, Chicago, IL, USA
e-mail: samaro@luriechildrens.org

J. F. Sarwark, R. L. Carl (eds.), *Orthopaedics for the Newborn and Young Child*,
https://doi.org/10.1007/978-3-031-11136-5_41

is recommended to achieve early detection and intervention. Other complications that contribute to mortality and morbidity include omphalocele, hyperinsulinemia, and macroglossia that could potentially cause airway obstruction. The incidence of BWS has not yet been correlated with race or gender. It is commonly diagnosed in early childhood.

Common Clinical Presentation

Providers should obtain a thorough history and focus on the family history of childhood cancers. This may help identify patients at even greater risk for tumor development. A physical exam in a patient with BWS may reveal overgrown characteristics such as macroglossia, omphalocele, hemihypertrophy, higher on the weight curve, nephromegaly, or hepatomegaly. Other characteristics may include ear creases and/or pits and umbilical hernia.

The phenotypic expression of BWS is variable, and diagnosis is based on clinical signs. If the patient exhibits at least three clinical findings or two major findings with at least one minor finding, further testing may be warranted (Table 41.1).

As noted, macroglossia is the most common clinical feature found. Other common features include macrosomia, abdominal wall defects, organomegaly, ear creases and/or pits, and embryonal tumors.

Macrosomia is defined as pre- and/or postnatal growth greater than the 97th percentile and is found in greater than 95% of patients [4]. Overgrowth continues in early childhood but becomes less dramatic with increasing age [4].

Abdominal wall defects commonly include exomphalos, umbilical hernia, or diastasis recti. Organomegaly commonly includes the abdominal organs such as kidneys, liver, spleen, pancreas, and adrenal glands. Embryonal tumors generally develop in early childhood and most commonly include Wilms' tumor, neuroblastoma, adrenal carcinoma, hepatoblastoma, or rhabdomyosarcoma (Figs. 41.1, 41.2, 41.3, and 41.4).

Table 41.1 Phenotype expressions of BWS [4]

Major findings	Minor findings
• Macroglossia (present in >95% of patients) • Macrosomia (present in ~80% of patients) • Abdominal wall defects (present in 65% of patients) • Organomegaly (present in 50% of patients) • Hemihyperplasia (present in 30–35% of patients) • Embryonal tumors (present in ~7.5% of patients) • Visceromegaly • Cytomegaly • Renal abnormalities (malformations, medullary dysplasia) • Ear creases and/or pits (present in 30% of patients) • Positive family history of BWS	• Hypoglycemia in the neonate (present in ~40% of patients) • Facial nevus flammeus (present in 30% of patients) • Polyhydramnios • Prematurity • Midface retrusion and infraorbital creases • Structural cardiac anomalies or cardiomegaly • Diastasis recti

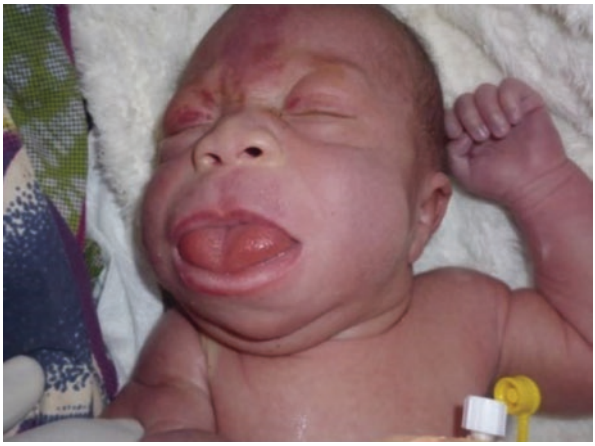


Fig. 41.1 Child with macroglossia and nevus flammeus. Reprinted from Mbuyi-Musanzayi S et al. (2014) Meningocele in a Congolese Female with Beckwith-Wiedemann phenotype. Case Rep Genet 2014:989425 989425 and found on the Forgotten Diseases Research Foundation Beckwith-Wiedemann Syndrome (BWS) website http://www.forgottendiseases.org/assets/Beckwith_Wiedemann_syndrome.html [5, 7]

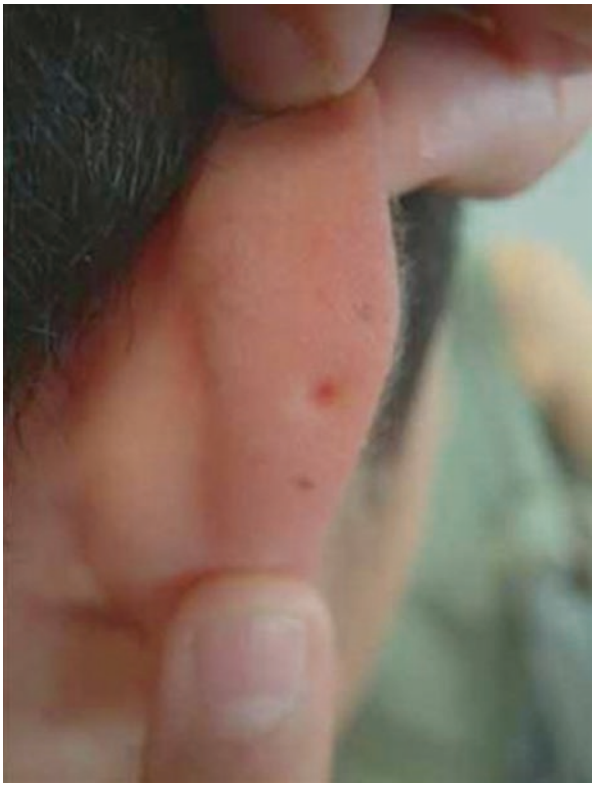


Fig. 41.2 Child with ear pits. Reprinted from National Human Genome Research Institute Elements of Morphology: Human Malformation Terminology. https://elementsofmorphology.nih.gov/index.cgi?tid=e9f6483380074c12 and found on the Forgotten Diseases Research Foundation Beckwith-Wiedemann Syndrome (BWS) website http://www.forgottendiseases.org/assets/Beckwith_Wiedemann_syndrome.html [6, 7]

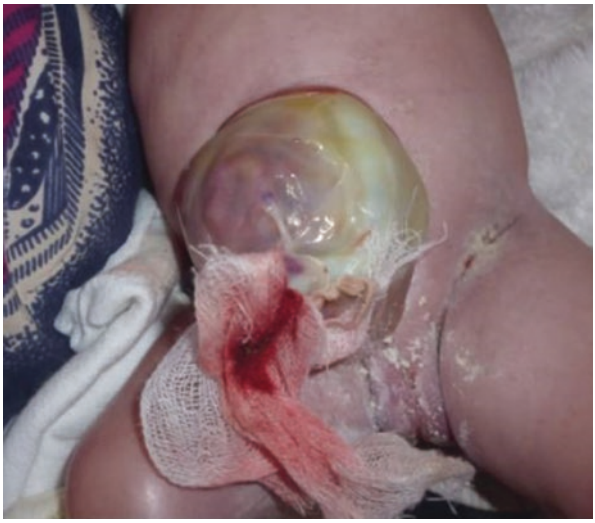


Fig. 41.3 Child with omphalocele. Reprinted from Mbuyi-Musanzayi S et al. (2014) Meningocele in a Congolese Female with Beckwith-Wiedemann phenotype. Case Rep Genet 2014:989425 and Forgotten Diseases Research Foundation Beckwith-Wiedemann Syndrome (BWS) and found on the Forgotten Diseases Research Foundation Beckwith-Wiedemann Syndrome (BWS) website http://www.forgottendiseases.org/assets/Beckwith_Wiedemann_syndrome.html [5, 7]

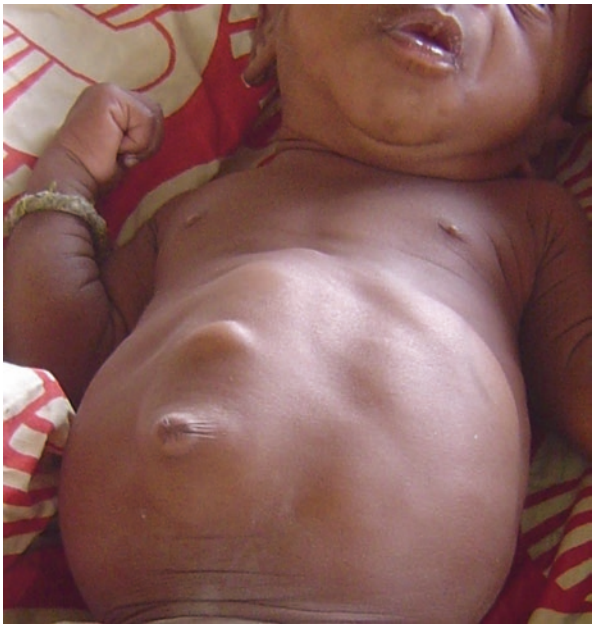


Fig. 41.4 Child with diastasis recti. Reprinted from Wikimedia Commons. Photo by Wikigil (https://commons.wikimedia.org/wiki/File:Hernie_ligne_blanche.JPG) and found on the Forgotten Diseases Research Foundation Beckwith-Wiedemann Syndrome (BWS) website http://www.forgottendiseases.org/assets/Beckwith_Wiedemann_syndrome.html [7, 8]

Evaluation

Beckwith-Wiedemann syndrome is considered a mosaic genetic disorder in which parts of the body have evidence of normal development of chromosome 11 while other parts of the body have cells with abnormalities on chromosome 11. Diagnosis should be based on clinical findings, genetic testing results, and positive family history. Diagnosis of BWS should be strongly suspected in patients who have three minor findings with at least two major findings, even if genetic testing is negative. Children should always be evaluated by a geneticist. Genetic testing can include DNA methylation studies, single-gene testing, chromosomal microarray (CMA), karyotype, and a multigene panel that includes CDKN1C [9].

DNA methylation studies of IC1 and IC2 should be performed simultaneously [9]. Methylation studies test for the attachment of methyl groups to DNA at cytosine bases [9]. Methylation of IC1 and IC2, specifically hypermethylation of IC1 and hypomethylation of IC2, is consistent with BWS. Since the methylation defects are mosaic, the test should be quantitative [10]. PCR-based methods are preferred because the DNA is modified with bisulfite, which converts unmethylated cytosines to uracil, inducing sequence differences between methylated and unmethylated DNA [10]. High-resolution melting analysis is another testing method, which also detects methylation differences in amplicons derived from bisulfite-modified DNA [10]. The advantages are that it is fast and cost effective and requires no post-PCR handling [10]. Single-gene testing can be considered in cases where there is a family history of BWS or with patients who have a strong clinical suspicion but do not have detectable cytogenic abnormalities in chromosome 11p15, copy number variants, or methylation abnormalities or if paternal uniparental disomy has been identified [10]. Uniparental disomy occurs when both copies of chromosome 11p15 are inherited from one parent versus inheriting one maternal and one paternal copy. Chromosomal microarray can detect a deletion or duplication of chromosome 11p15 and is also useful in detecting segmental paternal uniparental disomy [10]. Karyotype testing may be considered for an inversion or translocation of genes involving chromosome 11p15 [10]. Lastly, a multigene panel that includes CDKN1C can be used to identify deletion and duplication abnormalities as well as sequencing abnormalities [10]. CDKN1C is an abnormal mutation gene on chromosome 11.

Patients with BWS are at greater risk for tumor development; therefore, it is recommended to screen for tumors at the time of diagnosis. Common tumors found include Wilms' tumor and hepatoblastoma; therefore, routine renal ultrasounds, abdominal ultrasounds, and alpha-fetoprotein (AFP) serum levels are recommended. AFP elevation often precedes hepatoblastoma detection via ultrasound [11]. The overall incidence of tumor risk is about 5–10% in all patients diagnosed with BWS [11]. Patients with the gaining of methylation at IC1 were found to have a 28% incidence, while patients with a loss of methylation at IC2 were found to have a 2.6% incidence of tumor development [11]. Patients with CDKN1C

Table 41.2 Recommended cancer screening schedule [11]

	Begin screenings	Stop screenings	Testing	Frequency
Hepatoblastoma screening	Birth/ diagnosis	Fourth birthday	AFP serum levels, abdominal US, clinical exam	Every 3 months with clinical exams in between
Wilms' tumor screening	Birth/ diagnosis	Seventh birthday	Abdominal US to include kidneys and adrenal glands until 4 years of age. Begin renal US only, age 5–7 years	Every 3 months with clinical exams in between. After age 7, clinical exams are recommended annually

mutations have an incidence of 6.7% incidence of tumor risk [11]. Neuroblastoma screening is recommended for patients with CDKN1C mutations and includes urine catecholamines and chest X-ray [11] (Table 41.2).

Treatment/Management

Ongoing care of a patient with BWS will vary depending on the severity of clinical symptoms. Routine visits with a pediatrician are a must to monitor child development, and so proper referrals are made. Referrals to various specialists may be warranted. Regardless of severity, all children should be routinely screened for tumor development. Patients with significant macroglossia causing difficulties with speaking, feeding, or breathing may require a glossectomy or partial glossectomy. A plastic surgeon with experience in this procedure is preferred. Tumor development merits an oncology consult. Leg length discrepancy may be apparent in patients with hemihyperplasia, therefore warranting a consult by an orthopedic surgeon. A slight discrepancy in leg length generally does not require surgical intervention; however, more severe cases that cause a noticeable limp or make it difficult to perform daily activities may warrant epiphysiodesis. Epiphysiodesis is a procedure that can be performed in a few ways. The growth plate may be destroyed by drilling or scraping so that further growth is halted. Over time, the opposite leg continues to grow. The other way this can be performed is to place staples or a plate with screws around the sides of the growth plate to slow or stop growth. The staples or screws are then removed once the other leg has reached optimal length. External lengthening is also an option and involves the orthopedic surgeon performing an osteotomy in the shorter leg and applying an external fixator. The external fixator is secured with pins and allows for the patient or family member to turn a dial on the fixator causing the hardware to gradually pull apart. New bone will generate and fill the space created. Patients can generally expect to extend the affected limb approximately 1 mm/day.

Clinical Vignettes

Referrals to various specialists should always be considered in any patient who is suspected of having one or more symptoms of BWS. A geneticist familiar with BWS is a good place to begin. Prevention or early detection with common features in BWS are crucial and can greatly decrease mortality.

Natural History, Primary and Secondary Prevention

Patients with BWS have a good prognosis if complications are detected early. Early death may occur from complications of prematurity, hypoglycemia, cardiomyopathy, macroglossia, or tumors. The most common clinical feature is macroglossia, and without treatment, airway obstruction can be an issue causing obstructive apnea during feeding and/or sleeping. In milder cases of macroglossia, children tend to grow into their tongue and obstruction is not an issue. Abdominal wall defects are also common and can cause intestinal obstruction or malrotation of the gut. Omphalocele is also noted in some cases and without repair can cause sepsis, failure to thrive, vomiting, dehydration, and eventually death. Hypoglycemia is also prevalent and usually resolves with feeding; however, if left untreated, the patient can become unresponsive. Malignant tumor development may also occur, and early detection is preferred in order to decrease mortality. Early ultrasonography can detect many of the mentioned complications during the prenatal ultrasound. Prenatal ultrasonography can detect abdominal tumors, cardiac anomalies, omphalocele, nephromegaly, large for gestational age, and macroglossia.

References

1. Fontana L, Bedeschi MF, Maitz S, Cereda A, Faré C, Motta S, et al. Characterization of multilocus imprinting disturbances and underlying genetic defects in patients with chromosome 11p15.5 related imprinting disorders. Epigenetics. 2018;13(9):897–909. https://doi.org/10.1080/15592294.2018.1514230.
2. DynaMed Plus. Ipswich, MA: EBSCO Information Services. Record No. 116266, Beckwith-Wiedemann syndrome. 1995. http://www.dynamed.com/login.aspx?direct=true&site=DynaMed&id=116266. Accessed 25 Oct 2018.
3. Barisic I, Boban L, Akhmedzhanova D, Bergman JEH, Cavero-Carbonell C, Grinfelde I, et al. Beckwith Wiedemann syndrome: a population-based study on prevalence, prenatal diagnosis, associated anomalies and survival in Europe. Eur J Med Genet. 2018;61(9):499–507. https://doi.org/10.1016/j.ejmg.2018.05.014.
4. Gicquel C, Rossignol S, LeBouc Y. Beckwith-Wiedemann Syndrome. Orphanet encyclopedia. 2005. https://www.orpha.net/data/patho/Pro/en/BeckwithWiedemann-FRenPro260.pdf. Accessed 2 Nov 2018.

5. Mbuyi-Musanzayi S, Lubala Kasole T, Lumaka A, et al. Meningocele in a Congolese Female with Beckwith-Wiedemann phenotype. Case Rep Genet 2014;2014:989425. https://doi.org/10.1155/2014/989425.
6. National Human Genome Research Institute. Elements of Morphology: Human Malformation Terminology. https://elementsofmorphology.nih.gov/index.cgi?tid=e9f6483380074c12.
7. Forgotten Diseases Research Foundation. Beckwith-Wiedemann Syndrome (BWS). http://www.forgottendiseases.org/assets/Beckwith_Wiedemann_syndrome.html.
8. Wikimedia Commons. Photo by Wikigil. https://commons.wikimedia.org/wiki/File:Hernie_ligne_blanche.JPG.
9. Shuman C, Beckwith JB, Weksberg R. Beckwith-Wiedemann syndrome. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews®. Seattle, WA: University of Washington, Seattle; 2000. https://www.ncbi.nlm.nih.gov/books/NBK1394/.
10. Alders M, Bliek J, vd Lip K, vd Bogaard R, Mannens M. Determination of KCNQ1OT1 and H19 methylation levels in BWS and SRS patients using methylation-sensitive high-resolution melting analysis. Eur J Hum Genet. 2009;17(4):467–73. https://doi.org/10.1038/ejhg.2008.197.
11. Kalish J, Doros L, Helman L, Hennekam R, Juiper R, Maas S, et al. Surveillance recommendations for children with overgrowth syndromes and predisposition to Wilms tumors and hepatoblastoma. Clin Cancer Res. 2017;23(13):e115–22.

Chapter 42
Noonan Syndrome

Alison Murray

Brief Overview

Noonan syndrome was first described in 1962 by Jacqueline Noonan, a pediatric cardiologist, when she published a case series of nine patients who all had similar characteristics: pulmonary valve stenosis, small stature, mild intellectual disability, ptosis, undescended testes, skeletal malformations, and hypertelorism [1]. Since then, more information has been learned about the epidemiology and pathophysiology of this syndrome. Noonan syndrome has sometimes been called "male Turner's syndrome." However, while there are similar characteristics between patients with Turner's syndrome and patients with Noonan syndrome, the term "male Turner's" is a misnomer as Noonan syndrome is not a syndrome limited to males.

Background

The prevalence of Noonan syndrome is estimated to be 1 in 1000–2500 live births for severe phenotypes. However, as the phenotype can range in severity, some studies estimate that the syndrome can actually be as common as 1 in 100 live births when mild cases are included [2]. It is an autosomal dominant condition with complete penetrance but variable expressivity. However, 60% of cases are actually estimated to be a result of a de novo mutation.

A. Murray (✉)
Department of Pediatrics, Ann & Robert H Lurie Children's Hospital of Chicago, Chicago, IL, USA
e-mail: amurray@luriechildrens.org

J. F. Sarwark, R. L. Carl (eds.), *Orthopaedics for the Newborn and Young Child*,
https://doi.org/10.1007/978-3-031-11136-5_42

Noonan syndrome is caused by activating mutations in the RAS-mitogen-activated protein kinase (MAPK) pathway, a pathway essential for cell cycle differentiation, growth, senescence, and development. Half of known mutations are gain-of-function mutations on the protein tyrosine phosphatase non-receptor type 11 (PTPN11) gene on chromosome 12. This gene encodes the non-receptor protein tyrosine phosphatase SHP-2, which is involved in a wide variety of intracellular signal cascades downstream of receptors for growth factors, cytokines, and hormones [3].

While the majority of mutations occur in the PTPN11 gene, there are other gain-of-function mutations that can cause Noonan syndrome and some of the variation seen in clinical phenotype. These genes include SOS1, RAF1, and KRAS [4]. For instance, patients who have a PTPN11 gene mutation are more likely to have pulmonary stenosis and easy bruising and less likely to have hypertrophic cardiomyopathy in comparison to other genotypes. Ten to fifteen percent of cases of Noonan syndrome are due to a mutation in SOS1. Patients with this mutation have a similar spectrum of heart disease in comparison to patients with the PTPN11 gene mutation but are less likely to have short stature or to require special education. They are, however, more likely to have ectodermal mutations including curly hair, sparse eyebrows, or keratosis pilaris. RAF1 mutations account for 5–8% of cases of Noonan syndrome and are strongly associated with hypertrophic cardiomyopathy; 80–95% of patients with this mutation have HCM. The mutation can also be associated with a fatal course in infancy. KRAS mutations are rare as a cause of Noonan syndrome, only accounting for 2–3% of cases of Noonan syndrome. Cognitive impairments are more common in patients with KRAS mutations than are generally seen in Noonan syndrome.

Clinical Presentation

Appearance

Noonan syndrome facies are the most characteristic element of the syndrome, although these facial characteristics become subtler as the patient ages [3, 5]. Facial features include a high forehead, prominent widow's peak, and low posterior hairline. Patients also have relatively large heads, short uptilted noses, epicanthal folds, and downward-slanting palpebral fissures. The pillars of the philtrum are prominent, and they often have wide peaks to the vermillion border of the upper lip. They have low-set prominent ears that are posteriorly rotated and have a thickened upper helix. They usually have short necks and may have redundant skin. They also usually have broad chests with widely spaced nipples.

In childhood, the face may appear coarse or myopathic with prominent eyes, ptosis, and thick lips with prominent nasolabial folds. By the time of adolescence, the facial shape becomes more triangular with a wide forehead that tapers to a

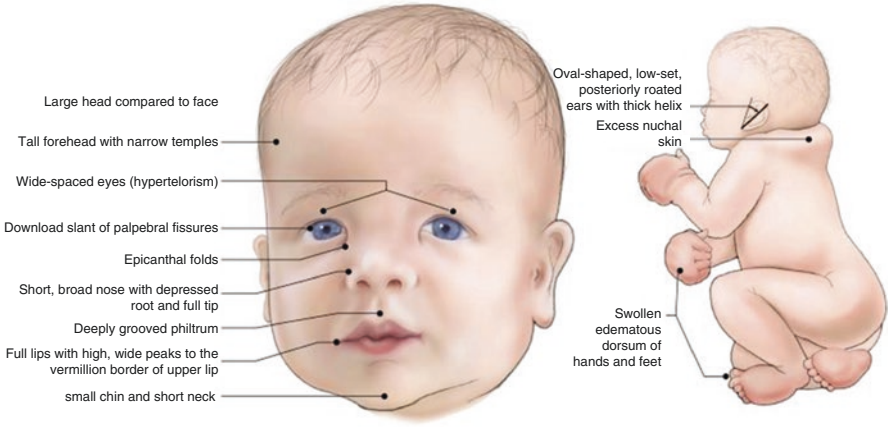


Fig. 42.1 Newborn with Noonan syndrome. Image reprinted from Darryl Leja, NHGRI, NIH

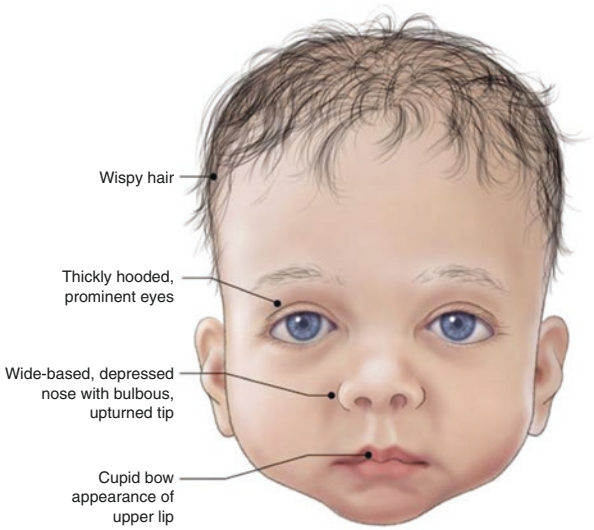


Fig. 42.2 Infant with Noonan syndrome. Image reprinted from Darryl Leja, NHGRI, NIH

pointed chin. In adolescence, the eyes also become more prominent, and the neck may appear less short. Older adults have prominent nasolabial folds, high anterior hairline, thick hooded eyelids, and wrinkled skin. Figures 42.1, 42.2, 42.3, and 42.4 show the progression of facial features through different ages.

The facial features described above are characteristic for Caucasian patients with Noonan syndrome. A study by Kruska et al. looked at the facial characteristics of patients with confirmed Noonan syndrome in non-Caucasian populations [6]. The three most common characteristics seen in all patient populations were widely spaced eyes, low-set ears, and short stature. Widely spaced eyes and low-set ears

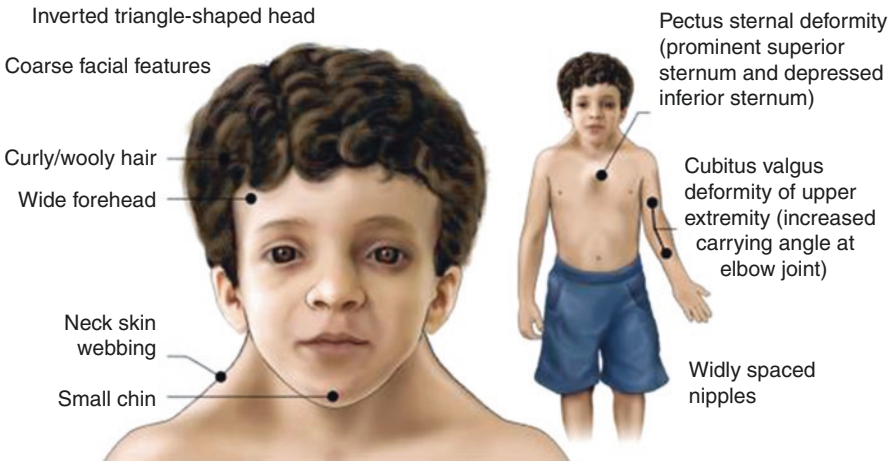


Fig. 42.3 Child/adolescent with Noonan syndrome. Image reprinted from Darryl Leja, NHGRI, NIH

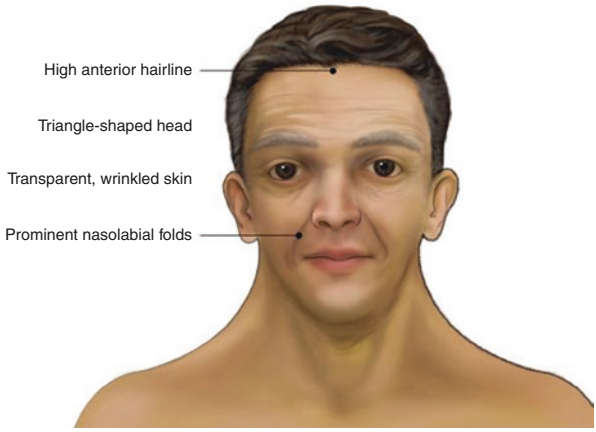


Fig. 42.4 Adult with Noonan syndrome. Image reprinted from Darryl Leja, NHGRI, NIH

were seen in 80% of the cohort, and short stature was seen in 70% of the cohort. The two characteristics statistically different between African-American, Asian American, and Latin American groups were ptosis and webbed neck, with both being more common in the Latin American population.

Cardiovascular

Noonan syndrome is the second most common syndromic cause of congenital heart disease, exceeded only by trisomy 21. Pulmonary valve stenosis is the most common cardiac anomaly seen in patients with Noonan syndrome and is seen in

50–62% of patients. Stenosis is most often caused by dysplastic leaflets and fibrous thickening of the annulus and leaflets. Supra-annular stenosis forms due to the fusion of the valvular cusp with the wall of the pulmonary artery [7]. Other congenital heart defects also occur in patients with Noonan syndrome, including secundum atrial septal defects (6–10% of patients), ventricular septal defects (5%), and persistent patent ductus arteriosus (3%). Peripheral pulmonary stenosis, atrioventricular canal, aortic stenosis, mitral valve stenosis, other mitral valve abnormalities, aortic coarctation, and coronary valve abnormalities have also been reported.

Hypertrophic cardiomyopathy is seen in about 20% of patients overall and is seen more frequently in patients with RAF1 mutations. The hypertrophy seen usually consists of asymmetrical septal thickening of the left ventricle or concentric hypertrophy and decreased left ventricular compliance [7]. Fifty percent of patients with Noonan syndrome also have an abnormal electrocardiogram with the most common findings being left axis deviation, abnormal R/S ratio of the left precordial leads, and an abnormal Q wave.

Endocrine

Fifty to seventy percent of patients with Noonan syndrome will have short stature. Their birth weight and length are typically normal, but they often have subsequent deceleration of height and weight until they are less than the third percentile. Similar to trisomy 21, there are specific Noonan syndrome growth charts that can be used. These patients also have normal growth hormone levels. Despite normal levels, in 2007, the USFDA approved treatment of short stature with recombinant human growth hormone. Treatment still remains controversial as patients with Noonan syndrome are at risk for hypertrophic cardiomyopathy and hematologic malignancies, and there is concern that the use of human growth hormone can increase this risk [8].

Puberty is typically delayed by 2 years for both males and females and is associated with a diminished growth spurt. Thyroid antibodies have also been seen in patients with Noonan syndrome, but there is no increased risk of hypothyroidism in comparison to the general population.

Renal/Genitourinary

Renal anomalies occur in 10–11% of patients with Noonan syndrome. The most common anomaly found is renal pelvis dilatation. Cryptorchidism also occurs in 80% of boys, and surgical orchiopexy is often required. Males have also been found to have fertility problems, thought to be secondary to Sertoli cell dysfunction, given that high FSH levels and poor sperm quality are seen in these patients [8].

Hematologic/Oncologic

Disordered bleeding is found to occur in 30–65% of patients with Noonan syndrome. Coagulation studies show prolonged bleeding times; factor VIII, XI, and XII deficiencies; thrombocytopenia; and platelet function defects. Symptoms associated with these abnormalities are often mild and include excessive bruising, epistaxis, and menorrhagia. However, bleeding associated with surgical procedures can be significant. The degree of abnormality in laboratory results does not correlate with the degree of symptoms. Surgeons should take precautions and be prepared for bleeding complications prior to any surgery performed on patients with Noonan syndrome.

Hepatosplenomegaly unrelated to cardiac disease has been reported to be present in 26–51% of infants with Noonan syndrome. Infants are also predisposed to transient monocytosis, thrombocytopenia, and myeloproliferative disorders. A 218C > T mutation in the PTPN11 gene is associated with a predisposition to myeloproliferative disorder, which most often resolves spontaneously [3].

Gastrointestinal

About 75% of infants had feeding difficulties [1]. These difficulties most commonly involved poor suck, prolonged feeding times, and recurrent vomiting. Twenty-five percent of infants needed to be fed by G-tube in order to gain appropriate weight.

Lymphatic

Noonan syndrome is associated with generalized disorder of lymphatic development and is seen from fetal life through adulthood. Peripheral lymphedema is most frequently seen in young infants. Lymphatic issues can present in other ways as well including hydrops, chylous pleural effusions, chylothorax, pulmonary lymphangiectasis, intestinal lymphangiectasis, hypoplastic leg lymphedema, anomalous lymphatic vessels in the thoracic cage, or aplasia/absence of the thoracic duct [1]. Lymphatic complications, especially chylous effusions, are also common after cardiovascular surgeries and surgeries to correct thoracic deformities [3].

Dermatologic

The most common dermatologic condition seen with Noonan syndrome is abnormal pigmentation, which includes pigmented nevi, café au lait spots, and lentigines [3]. Keratosis pilaris of the upper arms and face is also common and can impair hair and eyebrow growth.

Musculoskeletal

Patients with Noonan syndrome also have musculoskeletal abnormalities. The most common musculoskeletal deformity is a chest deformity with 70–95% of patients having pectus carinatum superiorly and excavatum deformity inferiorly. Cubitus valgus is seen in 50% of patients, and genu valgum has also been reported. Joint hyperextensibility is seen in 50%, clinobrachydactyly in 30%, talipes equinovarus in 12%, and radioulnar synostosis in 2% of patients [3]. Thirty percent of children have a spinal deformity, and surgical correction is recommended in two-thirds of these patients. Pigmented villonodular synovitis, a proliferative synovial lesion that involves the joints, tendons, and bursae, can occur and is often polyarticular.

Oral/Dental

Deontological issues associated with Noonan syndrome include high-arched palate, dental malocclusion, micrognathia, and articulation difficulties. Some patients may also develop mandibular cysts.

Neurologic/Ophthalmologic/Auditory

The most common structural CNS malformation seen in Noonan syndrome is Arnold-Chiari malformation type 1 and hydrocephalus.

Hearing loss can be associated with Noonan syndrome, and 10% of patients have auditory deficits in the low frequency range caused by sensorineural hearing loss, while 25% have deficits in the high frequency range [3]. Hearing loss due to otitis media is also a frequent complication, occurring in 15–40% of patients.

Up to 95% of patients with Noonan syndrome have an ophthalmologic abnormality, including strabismus, refractive error, amblyopia, or nystagmus. Two-thirds of patients have anterior chamber abnormalities, including cataracts. Fundal changes including optic head drusen, optic disk hypoplasia, and colobomas occur in 20% of patients [3].

Neurocognitive/Behavioral

The effects of Noonan syndrome on cognition are poorly understood and vary from person to person. In comparison to the general population, there is an increased incidence of cognitive issues and learning disabilities in Noonan syndrome. Most patients have normal intelligence with IQs ranging from 70 to 120, but 10–40% will require special education [1]. Early milestones may be delayed in patients, but this is often secondary to hypotonia and joint laxity. The average age for sitting is 10 months, walking alone is 21 months, and talking is 31 months [3].

Table 42.1 Van der Burgt Diagnostic Criteria [9]. Reprinted from Van der Burgt I, Berends E, Lommen E, Van Beersum S, Hamel B, Mariman E. Clinical and molecular studies in a large Dutch family with Noonan syndrome. American Journal of Medical Genetics. 1994;53(2):187–91, with permission from John Wiley and Sons

Feature	A = major	B = minor
1. Facial	Typical face	Suggestive faces
2. Cardiac	Pulmonary valve stenosis and/or typical ECG	Other defects
3. Height	<3rd percentile	<10th percentile
4. Chest wall	Pectus carinatum/excavatum	Broad thorax
5. Family history	First-degree relative suggests definite NS	First-degree relative suggests NS
6. Other	All three (males): mental retardation, cryptorchidism, lymphatic dysplasia	One of mental retardation, cryptorchidism, lymphatic dysplasia

Evaluation

Diagnosing Noonan syndrome is a clinical diagnosis, although molecular genetic testing can provide confirmation in 70% of cases. Van der Burgt et al. published diagnostic criteria in 1994 after studying a large Dutch family with Noonan syndrome [9]. These criteria include both major and minor features with a diagnosis occurring with a combination of major and minor features. Definite Noonan syndrome was considered 1A plus one of 2A-6A or two of 2B-6B; 1B plus two of 2A-6A or three of 2B-6B of the characteristics is shown in Table 42.1.

There are some nonspecific prenatal anomalies that are common in patients with Noonan syndrome including increased nuchal translucency, polyhydramnios, and abnormal maternal serum triple screen. The most common fetal anomaly seen is hydrothorax. The diagnosis of Noonan syndrome should be considered in fetuses that have normal karyotype and increased nuchal translucency, especially if there is a cardiac anomaly, polyhydramnios, and/or multiple effusions. In children, the diagnosis should be considered if two or more of the following are present: cardiac defect (especially pulmonary valve stenosis), short stature, chest deformity, intellectual disability, cryptorchidism, or a family history of any of the above.

Management

Treatment of Noonan syndrome depends on the clinical phenotype and thus varies from patient to patient. In patients with the clinical presentation of Noonan syndrome, consultation with a genetic counselor should occur to discuss the utility of genetic testing. PTPN11 should be the first gene sequenced given the prevalence, unless there are clinical features that point towards another gene mutation. If a child

is diagnosed with Noonan syndrome, the parents should also be tested to provide appropriate reproductive counseling for future pregnancies.

At the time of diagnosis, all patients should undergo a cardiac evaluation including electrocardiogram and echocardiogram. Further cardiac treatment depends on the type of cardiac lesion present. If there is no cardiac disease on initial evaluation, patients should be reevaluated every 5 years and require lifetime cardiac follow-up, as cardiac findings can occur at any point of time.

Children should be weighed and measured regularly by their primary care provider and appropriate growth charts used. If there is any evidence of growth failure, all underlying comorbidity conditions should be addressed, nutrition should be optimized, baseline labs should be performed, and referral should be made to a pediatric endocrinologist. Referral should also be made to a pediatric endocrinologist if puberty is delayed (no breast development in girls by the age of 13 and no testicular enlargement in boys by the age of 14).

Kidney ultrasound should be obtained at the time of diagnosis to look for any abnormalities. Antibiotic prophylaxis should be considered if hydronephrosis or recurrent urinary tract infections are present.

Pediatric gastroenterology or nutrition consults should be obtained if there are feeding difficulties or recurrent vomiting is present.

A screening CBC with differential, prothrombin time, and activated partial thromboplastic time should be performed at the time of diagnosis and at 6–12 months of age if the initial screen occurred during infancy. If bleeding symptoms occur, repeat labs should be obtained. If laboratory abnormalities exist, a hematology consult should be obtained followed by specific factor activity and platelet function testing. If a patient is having surgery, they should also have testing to evaluate bleeding risk. If splenomegaly or hepatomegaly is present, a CBC with differential ± liver function testing should be obtained. Patients should avoid aspirin and other aspirin-containing medicines if any coagulation abnormalities are found.

Patients with Noonan syndrome should have annual developmental screening with complete neuropsychological testing. Intervention should be obtained as applicable.

A detailed eye exam should be obtained in infancy or at the time of reevaluation every 2 years thereafter. Hearing test should also be obtained at infancy.

There should be annual examinations of the chest and back to assess for spinal abnormalities, with radiography if abnormalities are found on exam.

If peripheral lymphedema is present, the patient should be referred to specialty lymphedema clinics. The National Lymphedema Network can also be contacted (www.lymphnet.org) [10].

Patients with Noonan syndrome should be considered high risk for malignant hyperthermia if receiving general anesthesia.

There are several support groups for patients with Noonan syndrome. These include the Noonan Syndrome Support Group (www.noonansyndrome.org) [11], Magic Foundation (www.magicfoundation.org) [12], NORD: National Organization for Rare Disorders (www.rarediseases.org) [13], Human Growth Foundation (www.hgfound.org) [14], and BDF Newlife (www.bdfnewlife.co.uk) [15].

Summary

Noonan syndrome is a clinical diagnosis with a variable phenotype. The most common clinical characteristics are distinctive facies and cardiac and endocrinology abnormalities. Treatment depends on the clinical presentation but should be multidisciplinary.

References

1. Romano AA, Allanson JE, Dahlgren J, Gelb BD, Hall B, Pierpont ME, et al. Noonan syndrome: clinical features, diagnosis, and management guidelines. Pediatrics. 2010;126(4):746–59. https://doi.org/10.1542/peds.2009-3207.
2. Bhambhani V, Muenke M. Noonan syndrome. Am Fam Physician. 2014;89(1):37–43.
3. Van Der Burgt I. Noonan syndrome. Orphanet J Rare Dis. 2007;2:1–6.
4. Zenker M. Clinical manifestations of mutations in RAS and related intracellular signal transduction factors. Curr Opin Pediatr. 2011;23:443–51.
5. Turner AM. Noonan syndrome. J Paediatr Child Health. 2014;50:E14–20.
6. Kruszka P, Porras AR, Addissie YA, Moresco A, Medrano S, Mok GTK, et al. Noonan syndrome in diverse populations. Am J Med Genet Part A. 2017;173(9):2323–34.
7. Pierpont ME, Digilio MC. Cardiovascular disease in Noonan syndrome. Curr Opin Pediatr. 2018;1. http://insights.ovid.com/crossref?an=00008480-900000000-98960
8. Roberts AE, Allanson JE, Tartaglia M, Gelb BD. Noonan syndrome. Lancet. 2013;381(9863):333–42. https://doi.org/10.1016/S0140-6736(12)61023-X.
9. Van der Burgt I, Berends E, Lommen E, Van Beersum S, Hamel B, Mariman E. Clinical and molecular studies in a large Dutch family with Noonan syndrome. Am J Med Genet. 1994;53(2):187–91.
10. The National Lymphedema Network. www.lymphnet.org.
11. Noonan Syndrome Support Group. www.noonansyndrome.org.
12. Magic Foundation. www.magicfoundation.org.
13. NORD: National Organization for Rare Disorders. www.rarediseases.org.
14. Human Growth Foundation. www.hgfound.org.
15. BDF Newlife. www.bdfnewlife.co.uk.

Chapter 43
VACTERL Association

Sheila Chandran

Brief Overview

VACTERL association is a nonrandom association of birth defects that affect multiple body systems. The term is an acronym with the letter indicating the body systems involved: Vertebral defects, Anal atresia, Cardiac abnormalities, Tracheoesophageal fistula, Renal and Radial anomalies, and Limb defects. A single umbilical artery is also noted to be part of the association, and it has been proposed that "V" should also stand for vascular anomalies. Not all anomalies need to be present to diagnose the syndrome, and diagnosis is made with at least three characteristic features. Other features reportedly seen include dysmorphic facies, external ear malformations, laryngeal stenosis, choanal atresia, intestinal malformations, genital abnormalities, and tethered spinal cord. Some features are subtle and not identified later in life. Affected children may also exhibit failure to thrive. An important point to note is that intelligence and mental functioning are not affected.

Background Including Epidemiology and Pathophysiology

VATER association was initially described in the 1970s to term the statistic co-occurrence of Vertebral defects, Anal atresia, and Tracheo-Esophageal fistula with Radial and Renal dysplasia. After the initial description, the vascular and additional limb anomalies were identified, and the term VACTERL was coined. VACTERL association occurs sporadically in 1:10,000–40,000 newborns (approximately

S. Chandran (✉)
Department of Orthopedics, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA
e-mail: sheila.chandran@cchmc.org

J. F. Sarwark, R. L. Carl (eds.), *Orthopaedics for the Newborn and Young Child*,
https://doi.org/10.1007/978-3-031-11136-5_43

<1–9/100,000 infants), and large cohorts of patients have been described from all parts of the world [1].

Multiple genetic and environmental factors likely play a part but as of yet, relatively little is known about the etiology. The abnormalities are thought to result from defects in the mesodermal layer of the embryo during early fetal development. The current evidence suggests that there is still no evidence for a unifying cause that would lead to this condition being termed a syndrome [2]. VACTERL association is a diagnosis of exclusion. Multiple VACTERL features can be observed in chromosomal disorders, such as trisomy 18, Fanconi anemia, CHARGE syndrome, Holt-Oram syndrome, and Townes-Brocks syndrome.

Clinical Presentation: History and Physical

Vertebral Defects

Vertebral defects are seen in 60–80% of people with VACTERL association. These changes may include segmentation anomalies, such as hemivertebra, vertebral bars and blocks, or missing vertebra. Scoliosis may develop secondary to the underlying abnormalities and may be the first sign of vertebral anomalies. Rib abnormalities can be seen, including absent ribs, rib fusions, or supernumerary ribs. Some patients may require major surgical intervention for the vertebral anomalies, whereas other patients have no clinically significant findings. Regional anatomy is affected with patients with thoracic vertebral anomalies having higher association of TEF, while lumbar vertebral anomalies are seen in those with imperforate anus [3, 4]. Sacral agenesis may also occur.

Anal Atresia

Anal atresia is a condition in which a thin covering blocks the anal opening. Imperforate anus is when there is a failure of development of the passage between the rectum and the anus. Both will lead to blockage of the bowel and is noticed in newborn infants. These malformations occur in 55–90% of patients [1]. If the anus or rectum is involved, there is higher risk of genitourinary anomalies. Genitourinary anomalies occur in 25% of patients.

Cardiac Anomalies

Congenital heart anomalies have been reported in 40–60% of patients with VACTERL association. Ventricular septal defects are the most common, ranging from benign small openings that may close spontaneously to large life

life-threatening defects. Other congenital abnormalities seen include atrial septal defects, patent ductus arteriosus, transposition of the great vessels, tetralogy of Fallot, and hypoplastic left-heart syndrome.

Tracheoesophageal Abnormalities

Tracheoesophageal fistula (TEF) occurs in 50–80% of patients with VACTERL and may be present with or without esophageal atresia [5]. Signs and symptoms of early TEF include absent gastric bubble on prenatal exam, choking in infancy, or inability to pass nasogastric tube. Surgery is typically required in the first few days of life.

Renal and Radial

Lack of development or malformation of one or both kidneys can be seen in 50–80% of patients. Other collecting system abnormalities can predispose patients to have frequent urinary tract infections, nephrolithiasis, or hydronephrosis. Occult renal anomalies are important to diagnose as they can lead to declining renal function and severe morbidity.

The most obvious orthopedic abnormalities seen are the radial ray defect with poorly developed or missing thumbs or abnormal forearm musculature and hands. Five to ten percent of radial club hands are associated with VACTERL. Upper extremity limb anomalies range from hypoplastic thumb to radial club hand.

Limb (Non-radial) Abnormalities

Limb abnormalities are seen in 40–50% with VACTERL association, and there can be a wide degree of severity. Polydactyly, syndactyly, radioulnar synostosis, hypoplasia of the tibia or great toe, and clubfoot have all been described in patients with VACTERL association [3].

Single Umbilical Artery

The presence of a single umbilical artery should be noted as it is a frequent finding in patients with VACTERL association. The exact prevalence is unknown. This finding can be seen on prenatal ultrasounds and may be the first sign of the VACTERL diagnosis.

Evaluation

No laboratory test exists to diagnose VACTERL association. Diagnosis is made on clinical grounds after excluding other causes. Microarray analysis testing is used in both the prenatal and postnatal settings, followed by routine karyotype, Fanconi anemia testing, and single-gene testing [6]. Antenatal ultrasound can detect certain features of VACTERL such as polyhydramnios and lack of a gastric bubble due to TEF or some cardiac, renal, limb, or vertebral anomalies.

Cognitive function in patients with VACTERL association is not affected. If there is concern for mental functioning, further evaluation should be warranted. CNS malformations may be associated and should be excluded [3].

Management

Patients with anomalies that are incompatible with life, such as severe cardiac malformations, imperforate anus, and TEF, are typically diagnosed and treated in the first few days of life. Many other congenital anomalies will need to be followed by specialists to prevent morbidity.

Natural History, Primary and Secondary Prevention

The treatment of patients with VACTERL association is targeted towards the specific symptoms of each patient. With specialized care and improved surgical techniques, the prognosis of patients with VACTERL association has greatly improved compared to prior. However, even with early and successful intervention, severe malformations can cause patients to have numerous healthcare challenges throughout their life.

With regard to the orthopedic manifestations seen, each abnormality can be treated as an isolated problem. With vertebral malformations, MRI screening of the spine is recommended [7]. The key point is to recognize the association and the potential for later concerns.

As the cause of VACTERL is still unknown, further research to determine etiology can help continue to improve the health of affected patients.

References

1. Rittler M, Paz JE, Castilla EE. VACTERL association, epidemiologic definition and delineation. Am J Med Genet. 1996;63:529–36.
2. Raffel C, Litofsky S, McComb JG. Central nervous system malformation and the VATER association. Pediatr Neurosurg. 1990;16:170.

3. Lawhorn SM, McEwan GD, Bunnell WP. Orthopaedic aspects of the VATER association. J Bone Joint Surg Am. 1986;68:424.
4. Wulfsberg EA, Phillips-Dawkins TL, Thomas RL. Vertebral hypersegmentation in a case on the VATER association. Am J Med Genet. 1992;42:766.
5. Solomon BD, Bear KA, Kimonis V. Clinical geneticists views of VACTERL/VATER association. Am J Med Genet. 2012;158A(12):3087–100.
6. Solomon BD, Pineda-Alvarez DE, Raam MS, Cummings DA. Evidence for inheritance in patients with VACTERL association. Hum Genet. 2010;127:731–3.
7. Chan G, Dormans JP. Update on congenital spinal deformities: preoperative evaluation. Spine. 2009;34(17):1766–74.

Chapter 44
Musculoskeletal Manifestations of Mucopolysaccharidoses

Kathryn Oelsner and Merritt E. Adams

Mucopolysaccharidoses vary in the extent and specific type of skeletal manifestations, but almost always present with some form of radiologically identified dysostosis multiplex [1, 2]. Dysostosis multiplex specifically refers to abnormally shaped vertebrae and ribs, enlarged skull, spatulate ribs, hypoplastic epiphyses, thickened diaphysis, and bullet-shaped metacarpals [2]. Subtypes I–III are the most common at approximately 1/40–50,000, but most are exceedingly rare with epidemiologic rates of occurrence being <1/100,000. All are inherited autosomal recessive, except type II (Hunter), which is X-linked recessive. There is no primary or secondary prevention at this time. Pathogenesis varies somewhat for each subtype, but clinical manifestations occur secondary to the accumulation of glycosaminoglycans in various tissues. This is speculated to be due to various enzymatic errors in the degradation of acid mucopolysaccharide, causing its accumulation [1, 3, 4].

Initial presentation of orthopedic and other clinical symptoms varies dependent on specific disorder, but most present early.

K. Oelsner
Department of Pediatrics, University of Tennessee-Chattanooga, Erlanger Hospital, Chattanooga, TN, USA
e-mail: kathryn.oelsner@erlanger.org

M. E. Adams (✉)
Department of Orthopedic Surgery, Children's Hospital at Erlanger, UT College of Medicine Chattanooga, Chattanooga, TN, USA
e-mail: merritt.adams@erlanger.org

J. F. Sarwark, R. L. Carl (eds.), *Orthopaedics for the Newborn and Young Child*,
https://doi.org/10.1007/978-3-031-11136-5_44

Chronology of Typical Initial Orthopedic Manifestations (Figs. 44.1 and 44.2)

Mucopolysaccharidoses characteristically always involve some forms of orthopedic manifestations, including coarsening of facies, joint contractures, vertebral changes, diminished height, and chest wall abnormalities [3, 4]. Table 44.1 is specifically broken down into specific clinical orthopedic manifestations for each of the seven subtypes:

In addition to classic orthopedic complications, patients with MPS tend to have involvement of other organ systems, resulting in ocular, cardiac, respiratory, dermatologic, and gastrointestinal manifestations [3, 4]. In general, the cardiorespiratory complications tend to result in the highest morbidity, but blindness and deafness decrease quality of life. Umbilical and inguinal hernias ultimately result in surgical intervention.

Ocular: Types I, IV, V, VI, and VII are characterized by corneal clouding, which is typically progressive. Types II and III are distinctly characterized by a clear cornea. Types I, II, IV, and V also demonstrate pigmentary retinal degeneration ultimately resulting in loss of vision. Glaucoma has been reported in types IV, V, and VI and papilledema in type II.

Auditory: All MPS types are associated with hearing loss or deafness.

Respiratory/Upper Airway: Types I and II are characterized by noisy respirations and mucoid rhinorrhea. Frequent upper respiratory infections and acute otitis media have been reported in type IV.

Cardiac: All except type III have identified cardiac manifestations, including intimal thickening of coronary vessels or valvular involvement. Most of these types are associated with a cardiac murmur on exam.

Hepatic/Gastrointestinal: All except type III are associated with some form of hepatomegaly. Splenomegaly is additionally seen in types I, II, VI, and VII. Inguinal and umbilical hernias are additionally noted in all types except type III.

Dermatologic: Hirsutism or abundance of fine body hair is noted in types I, II, III, and V. Patients with type II may additionally have thicker skin than typical and nodular skin lesions on arms and posterior chest.

Evaluation for MPS consists of urine and blood samples to identify excess mucopolysaccharides as well as X-ray imaging to identify unique orthopedic manifestations. Assays to detect dermatan sulfate, heparan sulfate, and keratan sulfate simultaneously in blood samples have been developed [3–5]. Table 44.2 shows lab and X-ray findings.

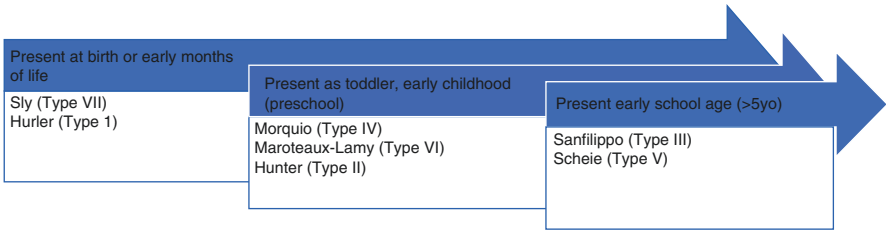


Fig. 44.1 Timeline of presentation for MPS

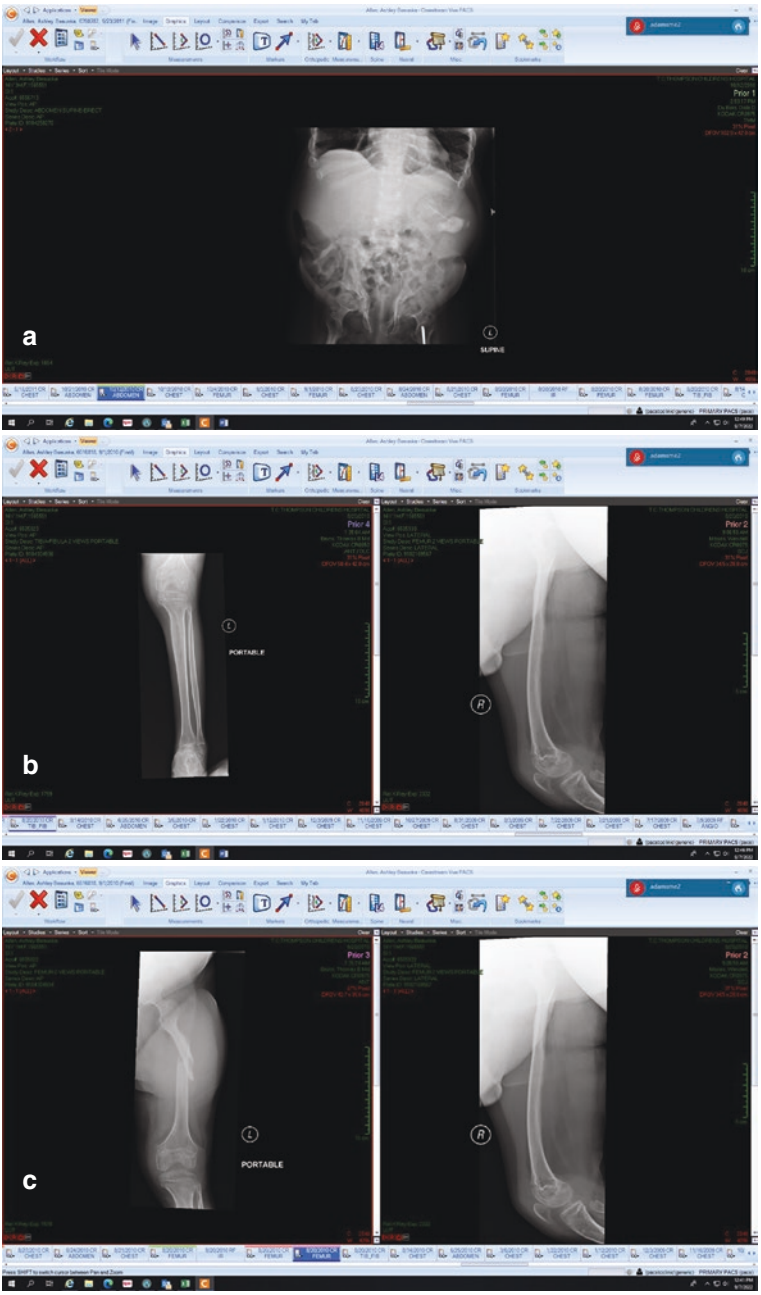


Fig. 44.2 These X-rays are from a patient with Hurler syndrome. The AP pelvis **(a)** shows the abnormal shape of the pelvis as well as acetabular protrusion; a hardware in place from the femur fracture is also shown. AP of the left femur **(b)** shows a fracture through the shaft. The tibia/fibula **(c)** shows an abnormal ankle joint, and there is abnormal mineralization of the bones, shown in all three X-rays (**a**, **b**, and **c**)

Table 44.1 Table of orthopedic manifestations, including facial features, vertebral features, joints, extremities, chest wall and truncal, and height features

Type of MPS	Facies/head	Vertebrae/spinal column	Joints	Extremities	Chest wall/trunk	Height
I (Hurler)	– Scaphocephalic macrocephaly (frontal prominence – Coarse[a] – Small misaligned teeth – Short neck – Hypoplasia of mandibular condyles – J-shaped sella turcica	– Odontoid hypoplasia – Kyphosis – Thoracolumbar gibbus (anterior vertebral wedging and beaking[b])	– Stiff – Limited mobility especially at phalanges, elbows, shoulders, hips causing carpal tunnel, claw hand, hip dislocation	– Diaphyseal broadening of short, misshapen bones (especially upper extremity)	– Flared rib cage – Widened medial clavicle	– Normal or excessive growth in first year, decline between 6 and 18 months – Short stature by 3 years old – Adult height: 118 cm
II (Hunter)	– Scaphoid macrocephaly – Coarse – Widely spaced teeth, delayed tooth eruption – Short neck	– Straight spine, possible kyphosis – Minimal vertebral changes	– Stiff – Joint contractures eventually causing immobilization (claw hand) – Hip degeneration	– Osteoarthritis of femoral head – Broadened bones	– Mild pectus excavatum – Pes cavus	Excessive growth in first 1–2 years, growth failure between 1 and 4 years old – Adult height: 120–150 cm
III (Sanfilippo)	– Macrocephaly with dense calvarium – Mildly coarse – Synophrys	Similar to MPS I, but milder	None	None	None	Normal at birth, minimally affected
IV (Morquio)	– Normal skull – Mildly coarse – Prominent lower face – Enamel hypoplasia in deciduous secondary teeth – Short neck	– Odontoid hypoplasia → atlantoaxial subluxation – Kyphoscoliosis – Lumbar lordosis – Marked platyspondyly (ovoid or flattened with anterior projection)	– Laxity and subluxation of joints (especially at wrists, small joints) – Restricted in larger joints (especially hips)	– Genu valgum – Short curved long bones with irregular tabulation, wide metaphyses with conical base, abnormal femoral neck, flat femoral head	– Short trunk – Wide ribs – Flared lower rib – Pectus carinatum	Marked growth retardation by 18 months old (usually onset between 1 and 3 years old) – Adult height: 82–115 cm

Table 44.1 (continued)

V (Scheie)	– Coarse by 5–8 years old – Mandibular prognathism – Short neck	None	– Stiffness begins in early school age (especially phalanges, elbows, shoulders) – Carpal tunnel	None	None	– Mildly impaired
VI (Maroteaux-Lamy)	– Macrocephaly – Slowly progressive coarsening by early school age – Enlarged sella turcica	– Odontoid hypoplasia – Lumbar kyphosis – Mildly flattened vertebrae with anterior wedging of T12 and L1	– Slowly progressive stiffness and limitation ultimately causing claw hand and carpal tunnel	– Genu valgum – Small carpal bones, broad short hands/feet – Metaphyses slightly broad and irregular – Femoral head dysplasia – Femoral epiphyses irregular or fragmented	– Prominent sternum – Broad ribs	– Growth retardation noted by 2–3 years old
VII (Sly)	– Macrocephaly – Coarse – J-shaped sella turcica	– Odontoid hypoplasia – Anterior and inferior beaking of lower thoracic and lumbar vertebrae – Thoracolumbar gibbus	– Joint contractures – Acetabular dysplasia with narrow sciatic notch	– Metatarsus adductus – Pointed proximal metacarpals – Hypoplastic basilar portion of ilia	– Flared lower ribs – Wide ribs – Prominent sternum	Postnatal growth deficiency

[a]Coarse features include full lips, flared nostrils, depressed/deep nasal bridge, macroglossia, hypertelorism

[b]Beaking: hypoplasia of anterosuperior area of the lower thoracic and upper lumbar vertebral bodies causing ovoid vertebrae, which looked beaked on lateral radiograph

Table 44.2 Lab findings and X-ray findings

	Lab findings		
Type of MPS	Urinary excretion	Cell staining	X-ray findings
I (Hurler)	Dermatan sulfate and heparan sulfate	– 10–60% leukocytes: metachromatic staining granules – Metachromatic staining fibroblasts – Urine, plasma, and cultured fibroblasts contain CF for MPS II, III, and VI	– Scaphocephaly – "Shoe-shaped" sella – Diaphyseal widening of tubular bones (especially in upper limbs) – Expansion of rib shaft – Anterior beaking of vertebrae
II (Hunter)	Increased excretion of acidic mucopolysaccharides with excess dermatan sulfate and heparin sulfate	– Metachromatic staining of leukocyte granules and fibroblasts – Urine, plasma, and cultured fibroblasts contain CF for MPS I, III, V, and VI	– Scaphoid skull – Enlarged sella with anterior excavation – Skeletal findings of dysostosis multiplex[a] – Minimal vertebral changes – Precocious osteoarthritis of femoral head
III (Sanfilippo)	Heparan sulfate	– Metachromatic staining of fibroblast and lymphocyte granules – Urine, plasma, and cultured fibroblasts with CF for MPS I, II, V, and VI	– Similar to MPS 1, but milder – Remarkably thickened calvarium – Limited sellar enlargement
IV (Morquio)	Keratosulfaturia, normal or increased total urinary AMPS excretion	– Granular inclusions in small percentage of granulocytes	– Vertebral flattening with central anterior projections in thoracic area and hook-shaped projections in lumbar area – Odontoid aplasia/ hypoplasia – Increased intervertebral space – Delayed ossification centers – Irregular epiphyses – Metacarpals' proximal pointing – Wide ribs – Osteoporosis – Normal skull

Table 44.2 (continued)

	Lab findings		
Type of MPS	Urinary excretion	Cell staining	X-ray findings
V (Scheie)	Excess dermatan sulfate	– Urine, plasma, fibroblast CX with CF for MPS II, III, VI – Fibroblast, leukocyte inclusions stain metachromatically	– Mild changes of dysostosis multiplex
VI (Maroteaux-Lamy)	Dermatan sulfate	– Metachromatic staining of fibroblasts and leukocyte inclusions – Urine, plasma, cultured fibroblasts with CF for MPS I, II, III, V	– Calvarium with greatly enlarged sella turcica – Fragmented epiphyses – Mild flattening of vertebrae with anterior wedging of T12 and L1 – Expanded ribs
VII (Sly)			– Short and anteriorly irregular vertebral bodies – Wedge deformities of lumbar vertebrae – Anterior and inferior beaking or lower thoracic and lumbar vertebrae

CF correction factor, *MPS* mucopolysaccharidoses

[a]Dysostosis multiplex: characteristic skeletal abnormality pattern in MPS disorders, including short and thick long bones with irregular hyperostotic shaft and metaphysis, widened ends to clavicles, flared iliac bones with flattened acetabulum and coxa valga deformity, narrow metacarpals proximally that widen distally, hypoplasia of anterosuperior areas of lower thoracic and upper lumbar bodies, "oar-shaped" ribs causing increased intercostal space, large skull with craniosynostosis and thick calvarium, and J-shaped sella turcica [2, 6]

There is no curative treatment of the mucopolysaccharidoses, but management often includes surgical correction of joint contractures, spinal fusions, hernia repairs, corneal transplants, cardiac valvular replacements, hearing aids, and physical therapy involvement. AAP published recommendations in 2007 and 2008 that all patients with mucopolysaccharidosis VI and I, respectively, should receive a baseline evaluation of neurologic, ophthalmologic, auditory, cardiac, respiratory, gastrointestinal, and musculoskeletal assessments and should be monitored every 6–12 months with individualized specialty assessments, to monitor disease progression and effects of intervention [5, 7]. Treatment of MPS I and VI now includes hematopoietic stem cell transplantation and enzyme replacement therapy (ERT). Treatment is most effective if started early before the irreversible damage [6].

The natural history of most MPS is early death from cardiorespiratory decompensation, secondary to intimal thickening of coronary vessels [2, 8]. Although clinical cases vary, most MPS types have some form of developmental delay. Type I usually demonstrates motor and mental developmental peak at 2 years of age with deterioration thereafter. Type II may have normal intellect, but with disruptive behavior. Type III is characterized by slowed mental development by 2–3 years of age, followed by behavioral disturbances and dramatic intellectual decline, with ultimate loss of motor and mental skills over time. Most are bedridden by age 20 with death by age 30. Types IV and VI are characterized by normal intellectual development, but early deaths by age 20 secondary to cardiorespiratory complications. Type V demonstrates little, if any, impaired intelligence. Type VII is characterized by moderately severe mental deficiency. If severe, patients with type VII may only survive months, but with mild cases, some patients may survive into adolescence [3, 4].

References

1. Cimaz R, La Torre F. Mucopolysaccharidoses. Curr Rheumatol Rep. 2014;16(1):389.
2. White KK. Orthopaedic aspects of mucopolysaccharidoses. Rheumatology (Oxford). 2011;50(Suppl 5):v26–33.
3. Jones KL, Jones MC, Campo MD, Smith DW. Smith's recognizable patterns of human malformation. 5th ed. Philadelphia, PA: Elsevier Saunders; 1996. p. 556–61.
4. Bergsma D. Birth defects: atlas and compendium. National Foundation-March of Dimes, Williams and Wilkins Co; 1972. p. 452–71.
5. Guigliani R, Harmatz P, Wraith JE. Management guidelines for mucopolysaccharidosis VI. Pediatrics. 2007;120(2):405–18.
6. Morishita K, Petty RE. Musculoskeletal manifestations of mucopolysaccharidoses. Rheumatology (Oxford). 2011;50(Suppl 5):v19–25.
7. Muenzer J, Wraith JE, Clarke LA. International Consensus Panel on the Management and Treatment of Mucopolysaccharidosis I. Mucopolysaccharidosis I: management and treatment guidelines. Pediatrics. 2009;123(1):19–29.
8. Tomatsu S, Fujii T, Fukushi M, Oguma T, Shimada T, Maeda M, et al. Newborn screening and diagnosis of mucopolysaccharidoses. Mol Genet Metab. 2013;110(1–2):42–53.

Chapter 45
Russell-Silver Syndrome

Sarah Carlson

Abbreviations

11p15.5	Hypomethylation of chromosome 11p15.5
GI	Gastrointestinal
ICR1	Imprinting center one
IV	Intravenous
LLD	Leg length discrepancy
RSS	Russell-Silver syndrome
SGA	Small for gestational age
UPD(7)mat	Maternal uniparental disomy for chromosome 7

Background

Russell-Silver syndrome, also known as Silver-Russell syndrome or RSS, was first described by Dr. Henry Silver, MD, in 1953 and subsequently Dr. Alexander Russell, MD, in 1954. Silver first presented two children who exhibited low birth weight, short statue, body asymmetry, and hemihypertrophy [1]. Dr. Russell independently presented a case study a year later, which included five children who had intrauterine growth retardation, triangular facial features, wide mouth with narrow lips, and body asymmetry [2]. In today's clinical practice, it has become common knowledge that patients with RSS have a combination of clinical presentations that both Russell and Silver presented years ago. Patients with RSS typically are born small for their

S. Carlson (✉)
Department of Orthopaedic Surgery, Ann and Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA
e-mail: scarlson@luriechildrens.org

J. F. Sarwark, R. L. Carl (eds.), *Orthopaedics for the Newborn and Young Child*,
https://doi.org/10.1007/978-3-031-11136-5_45

gestational age. RSS can be easily confused for a similar condition called SGA, or small for gestational age, which has similar characteristics but very different long-term outcomes. This can present challenges for RSS diagnosis. Therefore, it is very important that we know the difference between SGA and RSS.

Small for gestational age refers to a newborn whose birth weight and/or length is below the 2.3% percentile for weight and length when compared to the average weight and length for their gestational age. Children with SGA, but who are not also classified as RSS, potentially can recover growth as they get older; in fact, the vast majority of children with SGA will achieve full catch-up growth by the age of 2 years [3]. In contrast, Russell-Silver syndrome is characterized by intrauterine growth retardation followed by postnatal growth deficiency. The average height of males at adulthood is 151.2 cm, 4 foot 9 inches, and for females is 139.9 cm, 4 foot 2 inches [4]. Russell-Silver syndrome children all are characterized as being a part of the SGA population; however, they will not recover their growth loss, and they have other important physical characteristics that classify them as RSS. These characteristics could be as follows: relative macrocephaly, prominent forehead, body asymmetry, and feeding difficulties [5]. The RSS child can vary in the phenotype they present, as not all RSS children will have all of the same characteristics. Dr. Irene Netchine and Dr. Madeline Harbison, two leading physicians in the study and care of RSS patients, created a scoring system (see Table 45.1) for assistance in the diagnosis and management of RSS. Patients who score four of the six criteria meet the requirements for a diagnosis of Russell-Silver syndrome [5].

Table 45.1 Netchine-Harbison clinical scoring system [5]. The Netchine-Harbison clinical scoring system was created as a way to simplify the diagnosis of RSS. The patient must have at least four of the six criteria above. Using this scoring system in conjunction with molecular testing is the standard for Russell-Silver syndrome diagnosis. Reprinted from Wakeling E, Brioude F, Lokulo-Sodipe O, O'Connell S, et al., Diagnosis and management of Silver-Russell Syndrome: first international consensus statement, Nature Reviews Endocrinology, © 2017, Vol. 2, pgs. 105–124, with permission from Springer Nature [5]

Clinical criteria	Definition
SCA (birth weight and/or birth length)	≤–2 SDS for gestational age
Postnatal growth failure	Height at 24 ± 1 months ≤–2 SDS or height ≤–2 SDS below midparental target height
Relative macrocephaly at birth	Head circumference at birth ≥1.5 SDS above birth weight and/or length SDS
Protruding forehead	Forehead projecting beyond the facial plane on a side view as a toddler (1–3 years)
Body asymmetry	LLD of ≥0.5 cm or arm asymmetry or LLD <0.5 cm with at least two other asymmetrical body parts (one non-face)
Feeding difficulties and/or low BMI	BMI ≤–2 SDS at 24 months or current use of a feeding tube or cyproheptadine for appetite stimulation

Epidemiology

Russell-Silver syndrome is rare but has become a well-recognized condition associated with intrauterine growth retardation. Incidence rates of RSS range from 1:30,000 to 1:100,000 [5]. Russell-Silver syndrome is primarily diagnosed by the phenotype that it presents. There are many studies looking into a genetic cause to the condition; however, the complete incidence is still unknown.

Clinical Presentation

The diagnosis of RSS is primarily a clinical diagnosis; however, there is new research into a molecular cause for RSS, which will further help in confirming the diagnosis of RSS. RSS patients have many outstanding characteristics that set them apart from similar conditions. As mentioned above, Dr. Netchine and Harbison's scoring system seen in Table 45.1 presents the common characteristics of RSS patients. These characteristics are as follows: short stature, relative macrocephaly at birth, protruding forehead in early life, body asymmetry, typically hemihypotrophy, and feeding difficulties [5, 6]. Let us break this down further into specific features of the body.

Craniofacial

The craniofacial features present in RSS patients can be as follows: triangle-shaped face, where the face is shaped like an inverted triangle; abnormal ears, which are either low set or posteriorly rotated; a downturned mouth; and a thin upper lip [3].

The patient's chin and jaw tend to be smaller than someone who does not have RSS. The lower the weight of the patient, the more prominent these features can be. A good portion of patients who have RSS will require orthodontic work as they get older to help create room for their permanent teeth as they grow and to help reduce the chance for ear infections. Ear infections can be a common problem for patients due to the unusual angle and short length of the Eustachian tubes [3].

Another common feature of patients with RSS which can exacerbate feeding difficulties is that patients may have palate dysfunctions. Palate dysfunction can vary between high narrow-arched palate, overt cleft palates, and submucosa clefts [3]. Palate dysfunction may need to be repaired surgically to correct the problem. It is important to have an assessment done by a craniofacial team if you suspect that the patient has RSS.

Gastrointestinal

Another common clinical presentation in patients with RSS is the presence of gastrointestinal disorders. Digestive problems or malnutrition occurs in over 70% of the patients with SRS [5]. Generally, the first sign is the failure to thrive, which warrants a referral to a GI specialist as patients with RSS are already significantly below their peers on the growth charts for both height and weight. If there is a concern for proper nutrition, or decreased caloric intake, GI conditions should be evaluated further. RSS patients typically suffer from feeding difficulties, gastroesophageal reflux, delayed gastric emptying, and constipation. It is therefore very important to investigate GI problems aggressively and before the start of growth hormone, which typically occurs around the age of 2–4 [3]. If these GI problems have not been thoroughly investigated and addressed appropriately prior to the initiation of growth hormone therapy, then the outcome of the growth hormone treatment can be less than optimal and in certain cases highly ineffective.

Orthopedic

Russell-Silver syndrome patients will tend to have a wide variety of and frequent orthopedic concerns. There are some telltale signs beginning with hand anomalies. Most commonly, the patient's fifth finger will be shortened and curved towards the ring finger in a condition called clinodactyly. The middle phalanx is either shortened or wedge shaped, changing the fifth finger position to differ noticeably from that of the other fingers of the hand. This condition generally does not require treatment, and patients maintain normal function of their fifth finger. In a survey done by the MAGIC Foundation, they found that 90% of children had clinodactyly of the fifth finger bilaterally [3].

Body asymmetry is a common presentation in patients with RSS, most commonly leg length discrepancy. Body asymmetry typically occurs on one side of the body; this could include a shortened limb or a smaller circumference of the limb. Leg length discrepancy in a patient with RSS will likely present itself at birth. Patient's leg length discrepancy could be a result of a dislocated hip, shortened femur, shortened tibia/fibula, and a smaller foot on one side. Leg length discrepancy over 3 cm can lead to scoliosis and thus requires intervention [4].

Due to the presence of body asymmetry and more specifically leg length discrepancy in a large population of RSS patients, there is an increased likelihood for patients to develop scoliosis as a result. Scoliosis is naturally occurring in the general population and is far more common with patients who have a family history. Scoliosis usually presents itself following a growth spurt, and although it can be acquired, idiopathic, or congenital, most RSS patients fall within the acquired category. It is important for patients with RSS to walk with their hips even and aligned to help prevent the development of scoliosis.

In any patient with RSS, it is important for the patient to establish a good relationship with a pediatric orthopedic surgeon who is well versed in conditions such as leg length discrepancy, scoliosis, clinodactyly, and other common pediatric diagnoses.

Molecular Presentation

Although RSS is primarily a clinical diagnosis, there have been advancements on a molecular level to investigate a cause and a confirmation of the clinical diagnosis. In the consensus statement that came out in 2017, they created a flow chart to aid in the investigation and diagnosis of RSS (Fig. 45.1) [5]. As detailed in Fig. 45.1, molecular testing is used to confirm the diagnosis of RSS. As mentioned above, the clinical presentation of RSS can be very different in patients. Molecular diagnosis can be important in confirming the clinical diagnosis, particularly in milder cases.

RSS is a genetically heterogeneous condition characterized by either a hypomethylation of the paternal imprinting center 11p15.5 or a maternal uniparental disomy for chromosome 7 [4]. Of patients with RSS, 30–50% will present with the hypomethylation of the paternal chromosome, and 7–10% will have the maternal uniparental disomy for chromosome 7 [4–6].

Molecular presentation with a hypomethylation of the 11p15.5 chromosome is the most common, occurring in 30–50% of all patients with RSS. Hypomethylation is described as a loss of a methyl group on a particular DNA sequence [7]. During fetal development, the fetus receives one copy of each gene from each parent. These genes generally are considered active; however, when one gene is silenced, it can affect normal development. This silencing can occur on the maternal chromosome or the paternal chromosome. The 11p15.5 chromosome has a cluster of imprinted genes that are responsible for controlling fetal growth. In this particular molecular presentation of RSS, the hypomethylation of 11p15.5 chromosomes imprinting center (ICR1) occurs on the paternal allele. The ICR1 regulates the expression of H19 on the maternal allele and the expression of IGF2 on the paternal allele; in this instance, the H19 is overexpressed and the IGF2 is reduced resulting in a problem with fetal growth and development [5]. This is the most common form of molecular presentation in RSS patients; however, there is another molecular cause that is being investigated as a cause of RSS. Patients who have this particular molecular form generally will present with almost all of the typical characteristics of RSS, including being shorter and lighter at birth, and have more frequent body asymmetry [5].

Among RSS patients, 7–10% will test positive for another form of genetic changes that have been found to cause RSS. The other form of molecular presentation is called maternal uniparental disomy of chromosome 7, UPD(7)mat [4, 5]. The information present on this molecular presentation is far less than that of the 11p15.5. More clinical research is being done to further evaluate this chromosomal difference. It is important to know that if an RSS patient has only some of the clinical characteristics of RSS rather than a classic presentation of the syndrome, and he

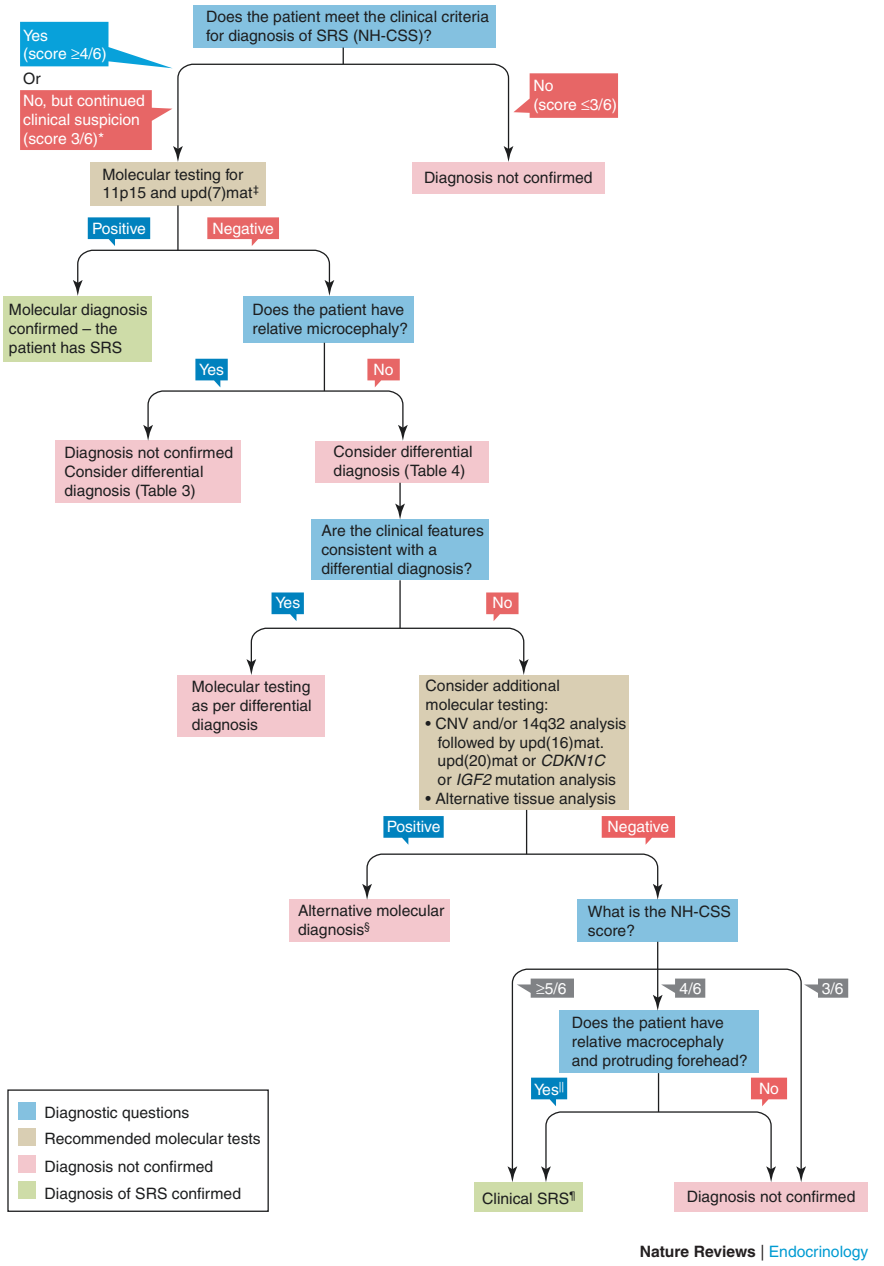


Fig. 45.1 Flowchart for investigation and diagnosis of SRS. This flowchart shows a systematic way of approaching a patient who presents with the clinical signs of Russell-Silver syndrome. As indicated, the blue boxes represent diagnostic questions. The tan boxes give you an indication as to when molecular testing would be good for further investigation of RSS [5]. The pink boxes do not confirm a diagnosis. The green boxes indicate a confirmation of RSS diagnosis. Reprinted from Wakeling E, Brioude F, Lokulo-Sodipe O, O'Connell S, et al., Diagnosis and management of Silver-Russell Syndrome: first international consensus statement, Nature Reviews Endocrinology, © 2017, Vol. 2, pgs. 105–124, with permission from Springer Nature [5]

or she presents with possibly less than the four out of six traits required by the Netchine and Harbison scoring system in Table 45.1 for diagnosing RSS; this would result in substantially more mild characteristics, and it might be helpful to undergo molecular testing whereby a positive test for maternal uniparental disomy of chromosome 7 could be helpful in the diagnosis since the classic presentation of RSS is not present [3]. Characteristics of RSS can be affected by having a particular molecular diagnosis. A patient with RSS that has a molecular diagnosis of UPD(7)mat typically will present with neurocognitive problems, such as global developmental delay or learning disabilities, than those who have a hypomethylation of 11p15.5 [5].

It is highly recommended that if there is a question on whether a patient might have RSS, the patient should be sent for genetic and molecular testing. Now that we have looked into the classic phenotype presentation, our next area of focus is on how a physician would manage a patient with RSS.

Management

Management for patients with RSS requires a multidisciplinary approach. It is very important that the patient establishes a rapport with a specialist who understands and recognizes the current and potential needs of an RSS patient. These specialists may include pediatricians, pediatric orthopedics, psychologists, gastroenterologists, craniofacial surgeons, endocrinologists, and dental specialists. Additional specialists that may be needed in some cases to provide care for a patient with RSS could include orthotists, physical therapists, occupational therapists, and speech therapists.

Once relationships have been established with the necessary specialists required for the specific needs and concerns of a particular individual RSS patient, the question becomes now what. Goals of treatment for a patient with RSS should have an emphasis on addressing specific clinical symptoms with the focus on optimizing growth, improving body composition, increasing appetite, and decreasing risk of hypoglycemia [5].

Growth Restrictions

One of the main concerns in patients with RSS is their ability to maintain and increase growth both in height and weight. Many RSS patients will be required to undergo treatment with growth hormones, which should be done under the close supervision of an endocrinologist. RSS is an indicator for the use of growth hormone; however, other indicators including caloric deficits need to have been addressed prior to initiating growth hormone therapy. Patients are generally between the ages of 2 and 4 when they begin therapy [5]. Special considerations should be taken to allow treatment with growth hormone before the age of 2 if the patient is experiencing severe hypoglycemia, severe malnutrition, and severe muscular hypotonia [4, 5]. In review of the research and the studies performed at the MAGIC Foundation, they have found that the overall use of growth hormone treatment has proven to be beneficial in children with RSS in optimizing their height [3].

Hypoglycemia

In addition to the use of growth hormone, it is important to be aware of the concern for RSS patients to be at risk of hypoglycemia. Hypoglycemia is characterized by extremely low blood glucose levels [8]. Onset of hypoglycemia is at its highest when the patient is young. Generally, times for hypoglycemia occur during physiological fasting, overnight fasting, illness, and use of general anesthesia and while on growth hormone [9]. Patients will be higher at risk for hypoglycemia due to the presence of a larger head when compared to their liver and muscle mass [3, 5]. Since many RSS patients have feeding difficulties and their caloric intake is less than adequate, hyperglycemia is a common concern. It is important to treat hypoglycemia through increased feedings, use of complex carbohydrates, dietary supplementation, and in severe cases initiating growth hormone treatment early [4]. The final consideration in the treatment of hypoglycemia is that if the RSS patient needs to undergo any type of surgical procedure, there should be a plan in place for prevention and treatment of hypoglycemia. The anesthesiologist, surgeon, and hospital staff should be included in this discussion, and treatment might include hospital admission the night before for monitoring of IV dextrose, pushing off any elective procedure until the patient is older, and care after surgery to prevent malnutrition [5]. Extreme caution should be taken to protect these patients from any unnecessary risk, and if surgery can be delayed, then it is advisable to do so.

Gastrointestinal

Gastrointestinal management includes a comprehensive evaluation of GI conditions that could be causing the patient's failure to thrive. Treatment may include nutritional support, prevention of hypoglycemia with increased frequency of feedings, use of complex carbohydrates, and possible speech therapy to work on feeding difficulties by increasing oral muscle tone and swallowing techniques. For common GI conditions such as gastroesophageal reflux, conservative treatment should be first considered. This would include eating smaller more frequent meals, changing feeding positions, lifting head up when laying in crib, medication intervention, and finally surgical considerations as a last resort. Constipation is common but can be easily treated with medication. The final condition of delayed gastric emptying is not as easy to treat and generally requires a surgical correction at this time as more research is needed in this area. Gastrointestinal conditions are hard to manage but are of vital importance in the understanding and appropriate treatment of this syndrome. If mistreated or not caught early, patients with RSS will have a harder chance to gain weight and improve height as proper nutrition and adequate caloric intake are not being met.

Orthopedic

Orthopedic management of RSS patients includes treatment for body asymmetry, leg length discrepancy, scoliosis, clinodactyly, hypotonia, etc. Treatment for these conditions should be monitored by a pediatric orthopedic surgeon. Common treatment for patients with leg length discrepancy (LLD) should include conservative treatment such as a heel lift or shoe buildup on the shortened side. Follow-up for LLD should be on a regular basis as the child grows; routine examinations may include X-ray studies using an AP leg length film. If the LLD continues to progress, surgical intervention may be warranted, which might mean a limb-lengthening procedure or an epiphysiodesis procedure to slow the growth of the longer limb. Careful monitoring of the patient's LLD is important, as a secondary process that can develop in patients with LLD is scoliosis.

Scoliosis is the curvature of the spine; it can be idiopathic in nature which has no known cause; congenital scoliosis is defined as "a sideways curvature of the spine that is caused by a defect that was present at birth" [10]. The third type of scoliosis is acquired scoliosis, which in RSS patients with LLD is generally the case. Scoliosis treatment includes routine X-rays to observe any progression in the curve. Scoliosis follow-up schedule can range from 4 to 6 months early in the assessment to further extend time as the child reaches skeletal maturity, which can be done then every 12 months. When a patient is evaluated for scoliosis, initial X-rays are usually done in a standing position, both an AP/PA scoliosis series and a full spine lateral. Both of these scoliosis series images should include the entire spine from head to hips, including the femoral heads. For follow-up, X-ray images are usually one-view AP/PA scoliosis series to limit radiation. If progression of the curve is seen, then referral to a pediatric spine surgeon who performs scoliosis correction surgery should be done.

Another orthopedic condition that might need management is when a patient has a smaller foot on one side, a form of asymmetry, and treatment may require the purchase of two different size shoes. There are stores such as Nordstrom or Von Maur that have discounts for patients that require two different size shoes due to a medical condition. For other conditions such as hypotonia or asymmetry, referral to a physical therapist for strengthening, core strength, and range-of-motion exercises is a good way to work on improving postural asymmetry and increasing muscle strength. Finally, the short stature, decreased size for gestational age, and increased size of the head in infancy can lead to RSS patients being delayed in areas like lifting their head off the ground, laying on their stomach, crawling, walking, and sitting up [9]. Working with an occupational therapist can help monitor these milestones and improve the likelihood that the patient will achieve them.

Psychosocial

Long-term management of patients with RSS can be complicated and difficult. RSS patients tend to face many challenges not only physically but socially as well. Very little information is available in the literature on RSS patients and psychosocial

issues of living with a rare disorder. Many RSS patients go on to live very successful and normal lives. It is important to learn the early warning signs for potential psychosocial conditions that can affect a child, adolescent, or adult. It is important to get a proper clinician for these patients who can help the child develop coping mechanism and problem-solving solutions that can help them as they navigate through life living with a rare disorder.

Conclusion

Russell-Silver syndrome patients face a long-term outlook that is generally good but will face many challenges from birth to adulthood. It is vital in the management of RSS that patients have a multidisciplinary approach to treatment, with clinicians that are fully aware of the symptoms and complications that RSS patients may face in their life. Key recommendations for diagnosis and management are as follows:

1. RSS is characterized by intrauterine growth restriction, postnatal growth retardation, triangular facial features, macrocephaly at birth, protruding forehead, body asymmetry, and feeding difficulties.
2. Early recognition and diagnosis are important in preventing feeding difficulties and gastrointestinal complications that can be a cause for postnatal growth retardation, poor appetite, oromotor issues, and low caloric intake.
3. If a patient is presenting with characteristics similar to RSS but may not have the necessary four out of six criteria for a confirmed clinical diagnosis according to the Netchine and Harbison's scoring system, genetic testing is highly recommended for assistance in confirming an RSS diagnosis.
4. Prevention of hypoglycemia by increased feedings, use of complex carbohydrates, dietary supplementation, and in severe cases initiating growth hormone treatment early.
5. For patients that present with the craniofacial concerns, it is important to build a relationship early with a craniofacial surgeon and orthodontic intervention to improve care and reduce the risk for feeding difficulties.
6. Pediatric orthopedic evaluation and management of symptoms including body asymmetry, leg length discrepancy, scoliosis, and hypotonia.

For further information on Russell-Silver syndrome, the MAGIC Foundation [11] is a great resource as the only non-for-profit organization dedicated to the care and treatment of patients and their families of Russell-Silver syndrome and other growth disorders. One other resource that patients may find informative on this condition would be the National Organization for Rare Disorders [12].

References

1. Silver HK, Kiyasu W, Deamer GJ, WC. Syndrome of congenital hemihypertrophy, shortness of stature and elevated urinary gonadotropins. Pediatrics. 1953;12:368–76.
2. Russell A. A syndrome of intra-uterine-dwarfism recognizable at birth with cranio-facial dysostosis; disproportionate short arms and other anomalies (5 examples). ProcSocMed. 1954;47:1040–4.
3. Salem JB. Defining key terms and the SGA/IUGR population, diagnosis Russell-Silver syndrome vs idiopathic small-for gestational-age. RSS/SGA a comprehensive guide. Understanding aspects of children diagnosed with Russell-Silver Syndrome or born small-for-Gestational-Age. Quadco Printing; 2009. pp 1–2, 11–12, 31–43, 18–19, 71–79.
4. Ardinger Adam MP, Pagon RA, et al., editors. Russell-Silver syndrome. Gene reviews. Seattle, WA: University of Washington, Seattle; 1993–2018. https://www.ncbi.nlm.nih.gov/books/NBK1324/. Accessed 7 Nov 2018.
5. Wakeling E, Brioude F, Lokulo-Sodipe O, O'Connell S, et al. Diagnosis and management of Silver-Russell syndrome: first international consensus statement. Nat Rev Endocrinol. 2017;13(2):105–24.
6. Netchine I, Rossignol S, Dufourg M-N, et al. 11p15 Imprinting Center Region 1 loss of methylation is a common and specific cause of typical Russell-Silver syndrome: clinical scoring system and epigenetic phenotypic correlation. J Clin Endocrinol Metab. 2007;92(8):3148–54.
7. Peinado M. Hypomethylation of DNA. Encyclopedia of cancer. 2011. https://link.springer.com/referenceworkentry/10.1007%2F978-3-642-16483-5_2923. Accessed 19 Nov 2018.
8. Demakis GJ. Hypoglycemia. In: Kreutzer JS, DeLuca J, Caplan B, editors. Encyclopedia of clinical neuropsychology. Cham: Springer; 2018. https://link.springer.com/referenceworkentry/10.1007/978-3-319-57111-9_558. Accessed 19 Nov 2018.
9. Salem JB. Defining key terms and the SGA/IUGR population, diagnosis Russell-Silver syndrome vs idiopathic small-for gestational-age. RSS/SGA a comprehensive guide. Understanding aspects of children diagnosed with Russell-Silver Syndrome or born Small-for-Gestational-Age. Quadco Printing; 2009. P 56–57, 85–87.
10. Congenital Scoliosis. 2010. https://orthoinfo.aaos.org/en/diseases%2D%2Dconditions/congenital-scoliosis/. Accessed 19 Nov 2018.
11. The Magic Foundation. https://www.magicfoundation.org/. Accessed 19 Nov 2018.
12. National Organization for Rare Disorder. https://rarediseases.org/rare-diseases/russell-silver-syndrome/. Accessed 19 Nov 2018.

Chapter 46
Moebius Syndrome

Annemarie Fox Kelly

Brief Overview of Condition

Moebius syndrome (MBS) is a rare neuromuscular disorder defined as "congenital, uni- or bilateral, nonprogressive facial weakness and limited abduction of the eye(s)" [1]. This facial diplegia occurs due to paresis or paralysis of cranial nerve VII and limitation of ocular abduction due to palsy of cranial nerve VI. Other clinical features may vary depending on other cranial nerves that may be involved. Commonly, Moebius syndrome is also associated with a wide variety of orofacial anomalies and axial and limb defects [2]. Although the prevalence of MBS is only estimated to be 1/100,000–1/250,000 live births, it remains an active topic for discussion in the literature due to the significant disfigurement and lifelong impairment that it causes and due to its still somewhat unclear pathogenesis [3].

Background Including Epidemiology and Pathophysiology

Moebius syndrome is estimated to occur as mentioned above in 1/100,000–1/250,000 live births with equal incidence in both sexes [3]. Most cases are sporadic in nature; however, a few familial inheritance patterns have been documented. There clearly is considerable heterogeneity in MBS, and genetics must only contribute partially to the pathogenesis of this syndrome.

A. F. Kelly (✉)
Department of Pediatrics, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA
e-mail: akelly@luriechildrens.org

J. F. Sarwark, R. L. Carl (eds.), *Orthopaedics for the Newborn and Young Child*,
https://doi.org/10.1007/978-3-031-11136-5_46

The pathogenesis of this syndrome is usually broken down into four leading theories:

1. Atrophy of the cranial nerve nuclei—likely related to disruption of the blood supply at the beginning of fetal development.
2. Destruction/damage of developed cranial nerve nuclei—caused by ischemia/lack of blood supply.
3. Problems of development of the peripheral nerves.
4. The facial muscles are the primary problem, and the atrophy of the nerves and their nuclei results from lack of stimulus from the non-functional muscles.

The first theory suggests that the subclavian and vertebrobasilar arteries fail to supply the developing hindbrain in the sixth week of gestation and inadequate blood supply to the cranial nerve nuclei results in ischemia and resulting malformation. This subclavian artery supply distribution sequence hypothesis has been used to explain the pathogenesis behind not only Moebius syndrome but Poland and Klippel-Feil syndromes as well [4]. Additionally, in support of a vascular insult is the association between conditions or teratogens that attenuate blood flow during pregnancy and MBS. Maternal infection (specifically rubella), vasculitis, and hyperthermia have all been linked with MBS. In addition, toxic in utero exposures to substances such as benzodiazepines, cocaine, thalidomide, and misoprostol have all been implicated as causative agents for MBS [5–7]. Most notably, the abortifacient misoprostol (a synthetic analogue of prostaglandin E1) when taken during the first trimester of pregnancy has been found to be strongly correlated with MBS, and in countries such as Brazil, where its use is more commonplace, MBS rates are much higher than in other areas throughout the world [8, 9].

The genetics underlying Mobius syndrome (MBS) are complex, and *most cases of MBS syndrome are sporadic*. In familial cases where a few cases have run in families, but there is no clear pattern of inheritance, there has been found to be a 2% inheritance risk of MBS with orthopedic anomalies. Without skeletal findings, the risk of inheritance is increased [10]. There are many genes involved in the development of the lower brain stem and nerve nuclei, and multiple chromosomal regions have been implicated in MBS with varying phenotypes. Specifically, four genetic loci have been most commonly described in association with Moebius syndrome: MSB1 on chromosome 13q12.2-a13, MSB2 on chromosome 3q21-q22, MSB3 on chromosome 10a21, and MSB4 on chromosome 1p22 [11]. These loci include genes that encode for motor neuron identification and migration. Specifically, the homeobox genes are expressed differentially in spatial and temporal patterns for rhombencephalon development. Creating mutations in the Hoxb-1 gene in murine models has resulted in a constellation of Moebius-type features with cranial nerve and craniofacial abnormalities [12].

Clinical Presentation

Moebius syndrome was defined at the Moebius Syndrome Foundation Research Conference in 2007 as "congenital, nonprogressive facial weakness with limited abduction of one or both eyes" [1]. Besides these two features, MBS has a wide variety of other clinical manifestations and often involves other cranial nerves, orofacial anomalies, and limb/axial malformations.

In an attempt to categorize and compare the phenotypes of MBS, Abramson et al. created a standardized grading system utilizing the mnemonic CLUFT [13] (Table 46.1).

We will utilize this structure to go through the heterogeneous clinical features.

Table 46.1 CLUFT grading system. Reprinted with permission from Abramson DL, Cohen Jr. MM, Mulliken JB; Mobius Syndrome: Classification and Grading System. Plastic and Reconstructive Surgery, Vol. 102/Issue 4, pages 961–970; ©1998;102:961–970; https://journals.lww.com/plasreconsurg/Citation/1998/09020/M_bius_Syndrome__Classification_and_Grading_System.4.aspx

Features	Grade
C: Cranial nerves	
– VIIth nerve partial	0
– VIth and VIIth partial	1
– VIth and VIIth complete	2
– Additional nerve involvement	3
– If bilateral and equal add	B
L: Lower extremity	
– Normal	0
– Talipes equinovarus, syndactyly, ankylosis	1
– Absent phalanges	2
– Longitudinal or transverse deficits	3
U: Upper extremity	
– Normal	0
– Digital hypoplasia or failure of differentiation	1
– Ectrodactyly	2
– Failure of formation, longitudinal or transverse	3
F: Facial structure anomaly	
– Normal	0
– Cleft palate	1
– Micrognathia	2
– Microtia, microphthalmia, abnormal joint, etc.	3
T: Thorax	
– Normal	0
– Scoliosis	1
– Pectoral hypoplasia or breast anomaly	2
– Chest wall deformity, breast or pectoral aplasia	3

C: Cranial Nerves

CN VII

The classic feature of facial nerve paresis or paralysis is evident shortly after birth. Facial paralysis results in a "masklike facies," and affected infants' faces remain essentially immobile even during bouts of crying or laughing. The facial nerve paralysis also results in an inability to fully close the eyelid or mouth and can result in excessive tearing or drooling. Infants have difficulty establishing a strong suck and can have difficulty latching and feeding due to weakness of the facial muscles [14]. Inability to close the eyelid fully (lagophthalmos) can result in exposure keratitis, conjunctivitis, and corneal abrasions.

CN VI

The next clinical criterion is abducens nerve impairment. This results in the inability of the eyes to abduct past midline. As a result, affected patients are forced to turn their head to follow objects. Vertical ocular movements are preserved, however.

CN XII

The third most commonly involved cranial nerve is the hypoglossal nerve in about one-fourth to one-third of MBS patients [15]. This can result in global hypoplasia and paralysis of the tongue and leads to significant dysphagia and dysarthria, especially when combined with palatal and pharyngeal paresis from glossopharyngeal nerve CN IX or vagal nerve CN X deficits. Often, patients can have difficulty eating and handling even their own secretions. Recurrent bouts of aspiration pneumonia can lead to dependency on tube feeding, especially early in life.

Other cranial nerves involved in MBS can include the trigeminal nerve (CN V) resulting in facial sensation abnormalities and difficulty chewing. CN III and CN IV, the extraocular and trochlear nerves, respectively, lead to ocular impairments other than the classic restricted lateral eye movements—notably ptosis, nystagmus, and strabismus. Less commonly, the vestibulocochlear nerve (CN VIII) and olfactory nerve (CN I) can be involved and lead to hearing and smell impairments, respectively [15].

L: Lower Extremity

Lower limb defects are very common in Moebius syndrome with more than half of patients reporting lower extremity anomalies [16]. In this same population surveyed, talipes equinovarus (clubfoot) was present in 40–60% of patients and next

common deformity was planovalgus. Syndactyly and brachydactyly are often present in about 20% of patients. Ankylosis or congenital vertical talus is present in about 5% of patients. Less common but still present were missing digits or transverse or longitudinal limb deficits. Additionally, muscular pain and complaints were common with many patients reporting nerve deficits (24%) and problems with weak or underdeveloped muscles [16].

U: Upper Extremity

In terms of upper extremity involvement, differences in digital anatomy with abnormal, missing, or shortened fingers were reported in >35% of polled patients. 18% of patients reported syndactyly. Nearly 30% of patients had nerve deficits in the upper extremities, and 17% of patients had stiffness in the arm and shoulder.

More severely, patients can have ectrodactyly (split hand), other digital anomalies, or terminal transverse or longitudinal limb defects [16].

F: Facial Structure

In addition to suffering from facial nerve palsy, Moebius syndrome patients can have many coexistent craniofacial abnormalities. Patients may have epicanthal folds, hypertelorism, flat nasal bridges, microglossia, micrognathia, and mandibular hypoplasia. Pierre Robin sequence (the combination of micrognathia, glossoptosis, and a high arched or cleft palate) has been reported in many patients [17]. Cleft palate alone has been reported in about 16% of MBS individuals. Dental abnormalities due to improper structure of the palate, jaw, and mouth are nearly universal. Ranked more severe on the spectrum of facial deformities, patients can even have microtia or microphthalmia (underdeveloped and small ears and eyes) [15]. These structural problems coupled with the nerve issues can result in significant functional difficulties in hearing or vision.

T: Thorax

Nearly a third (30%) of patients in McClure et al.'s orthopedic survey study of Moebius syndrome were diagnosed with missing or weak pectoralis muscles [16]. This association with chest wall deformities has spurred people to debate whether Moebius syndrome and Poland syndrome (characterized by unilateral absence of pectoralis major muscle, syndactyly, brachydactyly, and hypoplasia of the hand) represent distinct disorders or are a single entity "Poland-Moebius syndrome" [18]. Other thoracolumbar abnormalities include scoliosis in nearly 30% of MBS patients,

with over 10% with the diagnosis of kyphosis and 5% lordosis [16]. Missing, malformed, or fused vertebrae are documented as well. The degree of this scoliosis and its functional impairments to affected patients are not well documented in the literature, however. Additionally, both scapular and sternal abnormalities with atypical contour of the sternum, pectus excavatum, or pectus carinatum were present in nearly a fourth of surveyed patients.

Although this CLUFT mnemonic is helpful in breaking down many of the heterogeneous features of this syndrome, it is not fully comprehensive and does not give insight into the ramifications of above abnormalities and the significant developmental delays that patients may experience. I propose an addition to the mnemonic to be CLUFTeD with D representing delay.

D: Delay

Speech, motor, and possibly cognitive delays are common in Moebius syndrome, especially early in life. Some of these delays can be overcome with proper therapy; however, some persist into adulthood.

Speech Difficulties

As one can imagine with the various nerve palsies and craniofacial anomalies, articulation is challenging for patients with Moebius syndrome. Reduced oral sensitivity, incomplete lip closure, reduced tongue mobility, and weakened jaw musculature all can lead to difficulty with speech [19].

Motor Difficulties

Many patients report generalized hypotonia, balance impairment, and clumsiness lifelong in Moebius syndrome. Motor development and coordination often do not reach normal levels in adult age, even when skeletal deformities are taken into account. Verzijl et al. found that 88% of patients had generalized motor disability and 83% poor coordination in a large Dutch study. This was found to be consistent with MRI findings of hypoplasticity of the corticospinal or cortico-bulbo-cerebellar spinal tracts, signifying that the developing hindbrain is significantly impacted in MBS [20].

Moebius syndrome when found in combination with Pierre Robin sequence and generalized severe congenital hypotonia/myopathy is called Carey-Fineman-Ziter syndrome, but this has only been reported in less than 20 cases in the literature [21].

Cognitive Delay

Historically, studies proposed that there is a 10–15% incidence of intellectual disability that is usually mild in Moebius syndrome [2, 22]. However, recent analyses have suggested that in previous studies, the patients were not evaluated utilizing standardized scales to evaluate mental capacity and that in fact patients with MBS test within the normal range on intelligence, memory, and attention [23]. Perhaps more often than not, patients with MBS are falsely labeled as intellectually disabled due to their expressionless face, strabismus, excessive drooling, and difficulty with speech. The more debated topic is the true incidence of autism in MBS. Researchers from Sweden, Brazil, and Canada report a very high incidence of autism of up to 30%. However, studies from the Netherlands and the United States report rates similar to those in the general population (about 1%). Proposed etiologies for an increased rate in autism in MBS include brainstem maldevelopment or limited facial expressions stunting social interactions early in life [24, 25]. Limitations to these studies include that the DSM V diagnostic criteria for autism spectrum disorder include delayed speech and impaired social interaction that are both Moebius-related symptoms, not necessarily attributable to autism.

Evaluation and Management

Initial presentation of Moebius syndrome is usually very early on in life due to significant impaired facial and eye movements. The diagnosis is clinical based on having the characteristic two signs and symptoms, and there is no specific diagnostic test that can confirm a diagnosis of MBS [26]. Geneticists should be consulted to ensure that there is no alternative diagnosis and to give families an accurate assessment of risk of inheritance. There is no cure for Moebius syndrome, so treatment is aimed at giving patients the best quality of life possible. A multidisciplinary approach is usually best for patients with MBS, and many centers have craniofacial teams that can help patients with MBS immensely.

Speech therapy is essential for those with Moebius syndrome. Shortly after birth, speech language pathologists help infants with feeding difficulties. Specialized Haberman and other adapted bottles help overcome the difficulty with developing suction in the mouth. If infants are not able to utilize these specialized bottles appropriately, they may be dependent on nasogastric or tube feedings for nutrition. Speech therapists will watch for aspiration risks and thickened feeds if need be in order to prevent aspiration pneumonias [27]. Speech therapists will also work to help children work on articulation in order to help make speech understandable. Traditional speech therapy using visual and auditory stimuli and teaching compensatory postures is very helpful. Oral placement or muscle-based therapy adds tactile stimuli to teach the standard placement for speech and help with both consonant and vowel production [28].

Ophthalmologists are important specialists that patients with Moebius syndrome should see frequently. Due to lagophthalmos or inability to fully close the eyelid, the surface of the eye needs protection using eye drops and ointments, and sometimes eyelids need to be closed shut with tape or at least covered overnight. Exposure of the cornea can lead to exposure keratitis, ulceration, and visual loss if not addressed properly. When children are older, an upper eyelid gold-weight insertion is sometimes recommended to help the eyelid close by gravity [29, 30]. Surgery is often recommended for strabismus. Additionally, botulinum toxin injections to the medial rectus can aid strabismus surgery in achieving conjugate gaze.

Plastic surgeons are frequently involved in Moebius syndrome, especially when patients suffer from cleft palates. Facial reanimation or "smile" procedures have been successful in giving patients more natural expression and function of their mouth and smile. These are complicated surgeries and are performed through varying techniques (cross-facial nerve grafts, nerve transpositions, and muscle transfers) depending on the patient's anatomy [31, 32]. Orthodontists and maxillofacial surgeons are involved with mandibular hypoplasia and significant dental abnormalities.

Early involvement of orthopedists in the care of these patients is often necessary given the significant involvement of both upper and lower limb deformities. For the most common abnormality noted, talipes equinovarus (clubfoot) Ponseti casting technique is employed early. Even when recognized early and managed correctly, casting often fails and patients need posteromedial release (PMR) or surgical revision [16]. Conditions such as cleft hands or feet can sometimes be repaired surgically in order to improve the affected hand or foot's function and appearance. Various prostheses are used for transverse and longitudinal limb deficiencies, and physical therapists are utilized greatly in order to maximize function and coordination in these children.

Notably, patients with Moebius syndrome are at high risk for anesthetic complications given difficulty with airway and handling of secretions, not to mention their other comorbidities. A careful preoperative assessment is essential before embarking on any surgical procedure [33].

Lastly, psychologists and counselors are very helpful for patients with Moebius syndrome. Dealing with craniofacial deformities is challenging, and individuals are at risk for experiencing social and psychological stress as a result of their condition. As these patients can experience significant difficulty communicating with others, speech disturbances, and an inability to convey emotions through their face, those with MBS can have significant difficulty in social environments [34]. Interestingly enough however, a recent study found that adults with MBS rated themselves the same on anxiety, depression, and life satisfaction as their age-matched peers. The only area they reported lower was social competence [35]. This suggests significant resilience in this population who has faced much adversity, and despite the many challenges associated with living with MBS, many people with the condition live very successful professional and personal lives.

References

1. Mulliken JB. Mobius syndrome. NORD guide to rare disorders. Philadelphia, PA: Lippincott Williams & Wilkins; 2003. p. 223–4.
2. Briegel W. Neuropsychiatric findings of Moebius sequence—a review. Clin Genet. 2006;70:91–7.
3. Tenorio JD, Figueiredo MA, Espindula A, Gallottini M, Ortega KL. An interesting case of systemic lupus erythematosus in a patient with Moebius syndrome. Spec Care Dentist. 2018;38:112–5.
4. Bavinck JN, Weaver D, Opitz JM, Reynolds JF. Subclavian artery supply disruption sequence: hypothesis of a vascular etiology for Poland, Klippel-Feil, and Mobius anomalies. Am J Med Genet. 1986;23:903–18.
5. Puvabanditsin S, Garrow E, Augustin G, Titapiwatanakul R, Kuniyoshi KM. Poland-Möbius syndrome and cocaine abuse: a relook at vascular etiology. Pediatr Neurol. 2005;32(4):285–7.
6. Courtens W, Vamos E, Hainaut M, Vergauwen P. Moebius syndrome in an infant exposed in utero to benzodiazepines. J Pediatr. 1992;121:833–4.
7. Elsahy NI. Moebius syndrome associated with the mother taking thalidomide during gestation. Case report. Plast Reconstr Surg. 1973;51:93–5.
8. Pachajoa H, Isaza C. First case of Moebius-Poland syndrome in child prenatally exposed to misoprostol. Neurologia. 2011;26:502–3.
9. Pastuszak AL, Schuler L, Speck-Martins CE, Coelho KE, Cordello SM, et al. Use of misoprostol during pregnancy and Mobius syndrome in infants. N Engl J Med. 1998;26:1881–5.
10. Kadakia S, Helman SN, Schwedhelm T, et al. Examining the genetics of congenital facial paralysis—a closer look at Moebius syndrome. Oral Maxillofac Surg. 2015;19:109–16.
11. Mobius PJ. Uber angeborenen doppelseitige Abducens-facialis-Lahmung. Munch Med Wochenschr. 1888;35:91–4.
12. Goddard JM, Rossel M, Manley NR, Capecchi MR. Mice with targeted disruption of Hoxb-1 fail to form the motor nucleus of the VIIth nerve. Development. 1996;10:3217–28.
13. Abramson DL, Cohen MM Jr, Mulliken JB. Mobius syndrome: classification and grading system. Plast Reconst Surg. 1998;102:961–70.
14. Redett RJ. A guide to understanding moebius syndrome. Children's Craniofacial Association. 2013. http://www.ccakids.com/moebius-syndrome.html. Accessed 17 Oct 2018.
15. Picciolini O, Porro M, Cattaneo E, Castelletti S, Masera G, et al. Moebius syndrome: clinical features, diagnosis, management and early intervention. Ital J of Pediatr. 2016;42:56.
16. McClure P, Booy D, Katarincic J, Eberson C. Orthopedic manifestations of mobius syndrome: case series and survey study. Inter J Pediatr. 2016;2016:9736723.
17. Gómez-Valencia L, Morales-Hernández A, Cornelio-García R, Toledo-Ocampo E, et al. Clinical and genetic study of Moebius syndrome. Bol Med Hos Infant Mex. 2008;65:1685–146.
18. Chopan M, Sayadi L, Laub D. Mobius syndrome and Poland syndrome presenting together in a single patient. Eplasty. 2015;15:ic12. eCollection 2015.
19. Meyerson MD, Foushee DR. Speech, language and hearing in Moebius syndrome: a study of 22 patients. Dev Med Child Neurol. 1978;3:357–65.
20. Verzijl HT, van der Zwaag B, Cruysberg JR, Padberg GW. Mobius syndrome redefined: a syndrome of rhombencephalic maldevelopment. Neurology. 2003;61(3):327–33.
21. Dufke A, Riethmüller J, Enders H. Severe congenital myopathy with Möbius, Robin, and Poland sequences: new aspects of the Carey–Fineman–Ziter syndrome. Am J Med Genet. 2004;127A:291–3.
22. Kuklík M. Poland-Möbius syndrome and disruption spectrum affecting the face and extremities a review paper and presentation of five cases. Acta Chir Plast. 2000;42:95–103.
23. Verzijl HT, Padberg GW, Zwarts MJ. The spectrum of Mobius syndrome: an electrophysiological study. Brain. 2005;128:1728–36.
24. Briegel W, Schimek M, Kamp-Becker I. Moebius sequence and autism spectrum disorders—less frequently associated than formerly thought. Res Dev Disabil. 2010;31:1462–6.

25. Briegel W, Schimek M, Kamp-Becker I, Hofmann C, Schwab KO. Autism spectrum disorders in children and adolescents with Moebius sequence. Eur Child Adolesc Psychiatry. 2009;18:515–9.
26. MacKinnon S, Oystreck D, Andrews C, et al. Diagnostic distinctions and genetic analysis of patients diagnosed with Moebius syndrome. Ophthalmology. 2014;121:1461–8.
27. Fairgray E, Miles A. Enhancing surgical outcomes: the effects of speech therapy on a school-aged girl with Moebius Syndrome. Int J Ped Otorh. 2016;90:58–62.
28. Rosenfeld-Johnson S. Oral placement therapy for adolescents and adults with the diagnosis of moebius syndrome. 2014. https://moebiussyndrome.org/wp-content/uploads/2015/07/SaraRJ-Speech-2014.pdf. Accessed 12 Oct 2018.
29. Lopez-Valverde G, Jarrin-Hernandez E, Cruz-Gonzalez F, Mateos-Sanchez E. Möbius syndrome: surgical treatment for eyelid dysfunction. Case Rep Ophthalmol. 2013;4(3):229–33.
30. Magli A, Bonavolonta P, Forte R, Vassallo P. Lower eyelid surgery for lagophthalmos in Mobius and Poland-Mobius syndromes. J Craniofac Surg. 2011;22:e53–4.
31. Morales-Chávez M, Ortiz-Rincones MA, Suárez-Gorrin F. Surgical techniques for smile restoration in patients with Möbius syndrome. J Clin Exp Dent. 2013;5(4):e203–7.
32. Byrne P, Kim M, Boahene K, Millar J, Moe K. Temporalis tendon transfer as part of a comprehensive approach to facial reanimation. Arch Facial Plast Surg. 2007;9:234–41.
33. Ferguson S. Moebius syndrome: a review of the anaesthetic implications. Paediatr Anaesth. 1996;6(1):51–6.
34. Strobel L, Renner G. Quality of life and adjustment in children and adolescents with Moebius syndrome: evidence for specific impairments in social functioning. Res Dev Disabil. 2016;53-54:178–88.
35. Bogart KR, Tickle-Degnen L, Joffe MS. Social interaction experiences of adults with Moebius syndrome: a focus group. J Health Psychol. 2012;17(8):1212–22.

Chapter 47
Ehlers-Danlos

Craig J. Finlayson

Background

Ehlers-Danlos syndrome is a heterogeneous group of inherited connective tissue disorders. The earliest known reference to the syndrome is thought to be from Hippocrates in 400 B.C., who noted Nomads with lax joints and multiple scars. It was recognized as a distinct syndrome by Edvard Ehlers in 1901 and further described by Henri-Alexandre Danlos in 1908. The genetic inheritance of the disease was recognized in the 1960s, and the first genetic defect was identified in 1972 [1]. Continuing research into the genetic basis of the syndrome and the various clinical manifestations has led to the definition of 13 subtypes in the most recent classification scheme [2].

Epidemiology/Pathophysiology

EDS is an inherited genetic disorder. The combined prevalence of all subtypes has been estimated to be at least 1 in 5000, with some more recent studies suggesting a prevalence as high as 0.75–2% [3]. Accounting for approximately 80–90% of EDC cases, the hypermobility subtype is by far the most common, while the rarer subtypes have only a few affected families or sporadic cases reported in the literature. EDS is usually inherited through autosomal dominant transmission although autosomal recessive inheritance has been reported in the rarer subtypes and even in the hypermobility subtype [4].

C. J. Finlayson (✉)
Division of Orthopaedics and Sports Medicine, Ann and Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA
e-mail: cjfinlayson@luriechildrens.org

J. F. Sarwark, R. L. Carl (eds.), *Orthopaedics for the Newborn and Young Child*,
https://doi.org/10.1007/978-3-031-11136-5_47

EDS subtypes have been linked to mutations in genes encoding several types of collagen (I, III, V, XII) as well as various proteins related to synthesis, intracellular transport, secretion, and assembly of extracellular matrix proteins. Classic EDS is due to a mutation in type V collagen. The genetic defect responsible for the hypermobile subtype remains unknown, although mutations in tenascin-X, encoded by the TNXB gene, have been found in several patients presenting with hypermobile EDS. The hypermobile phenotype likely represents significant genetic heterogeneity [4]. In all subtypes, the end result of these genetic mutations is fragility of the connective tissues leading to the myriad of clinical presentations of EDS.

Clinical Presentation

The clinical presentation of EDS varies considerably based on the subtype and specific gene defect, but the classic findings are hyperlaxity of the joints and skin. Repetitive joint injuries are common initial presenting complaints. In the young child, hypotonia and delayed neurodevelopment with respect to coordination and motor skills may be early manifestations [5]. In the older child or adolescent, chronic and widespread musculoskeletal pain may be the primary complaint. Rarer subtypes present acutely during the neonatal period with hip dislocation, clubfeet, kyphoscoliosis, or severe hypotonia. These neonatal presentations may be difficult to distinguish from other congenital syndromes such as Larsen's syndrome. Additional differential diagnosis in the neonate and young child includes osteogenesis imperfecta, Loeys-Dietz syndrome, mucopolysaccharidoses, cutis laxa, pseudoxanthoma elasticum, Ullrich congenital muscular dystrophy, and various skeletal dysplasias.

In addition to hyperlaxity of the skin and joints, patients with classical EDS may exhibit fragility of the blood vessels. This can result in easy bleeding or bruising, dilation of the aortic root, and even aortic dissection. Cardiac valve dysfunction including mitral and tricuspid valve prolapse may also be present. Cutaneous findings include atrophic scars, molluscoid pseudotumors (fleshy, calcified growths over joint surfaces), and subcutaneous spheroids (mobile, calcified bodies in the subcutaneous tissue). Facial features may include epicanthal folds, blue sclerae, micrognathia, and a high-arched palate.

The remaining subtypes have distinct clinical presentations that are described in Table 47.1 (see Fig. 47.1) [2].

Table 47.1 Clinical presentation subtypes

Hypermobile	Generally, less severe than classic EDS. Musculoskeletal issues, chronic pain, and dysautonomia are common. Chronic pain and musculoskeletal dysfunction may be associated with psychosocial impairment. Postural orthostatic hypotension (POTS) is a common manifestation of dysautonomia. Gastrointestinal involvement including irritable bowel syndrome and gastroesophageal reflux is also common. There is minimal risk of cardiac complications
Classical-like *Cardiac-valvular*	Similar to classic EDS but due to mutation in tenascin-X defect Severe cardiac defects are present with only minor signs of EDS
Vascular	May present at birth with clubfoot deformity and hip dislocation. Inguinal hernia and pneumothorax may also be encountered in childhood. There is high risk for arterial dissection and rupture. In addition to aneurysms, arteriovenous malformations such as carotid artery-cavernous sinus fistula may be present. Hollow organs such as the intestines and uterus are at risk for rupture
Arthrochalasia	High risk for major joint dislocations. May present with congenital hip dislocation and severe hypotonia. These patients may have difficulty achieving independent ambulation
Dermatosparaxis	Characteristic body type and features include short stature, loose skin, epicanthal folds, blue sclerae, and micrognathia. There is a propensity for hernias as well as rupture of the bladder. Closure of the fontanelles may be delayed
Kyphoscoliotic	In addition to kyphoscoliosis, ocular issues are prominent with the risk of retinal detachment, glaucoma, globe rupture, and vision loss. Hypotonia and congenital hip dislocations may also occur
Brittle cornea syndrome	Eye involvement includes risk of corneal rupture, degeneration, and protrusion. Blue sclerae may be present
Spondylodysplastic	Skeletal dysplasia with short stature, bowing of the extremities, flattened vertebral bodies, and tapered fingers
Musculocontractural	Muscle weakness and joint contractures predominate in this subtype. Developmental delay is common in this subtype. Congenital clubfeet and kyphoscoliosis may also be present
Myopathic	Myopathy present at birth with severe hypotonia. May also result in sensorineural hearing loss and scoliosis
Periodontal	Early-onset periodontal disease with potential for tooth loss

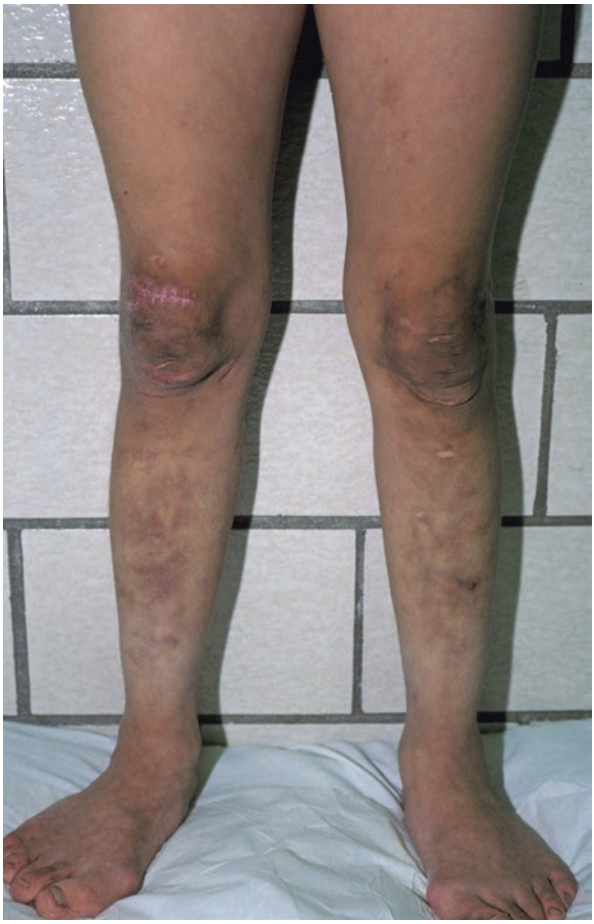


Fig. 47.1 Clinical photo demonstrating skin laxity, knee hyperextension, atrophic scarring, bruising, pes planovalgus, and bunion deformity

Testing

Diagnosis of EDS may be difficult in the neonate and infant. The presentation is more obvious in certain subtypes such as arthrochalasia or kyphoscoliosis, but the hypermobile subtype may be more subtle, resulting in delayed diagnosis. As such, hypotonia and developmental delay in conjunction with joint hypermobility should prompt the clinician to investigate the possibility of EDS.

Clinical criteria and genetic testing provide the basis for diagnosis. However, the most common subtype, hypermobile, lacks a specific genetic marker. Therefore, genetic testing may be useful to confirm certain subtypes of EDS or to rule out other genetic disorders from the differential, but the limitations of genetic testing must be recognized.

Hyperlaxity of the skin has been defined based on location. For the distal forearm and dorsum of the hand, greater than 1.5 cm is considered positive, and 3 cm is positive at the neck, elbow, and knee. The Beighton score is used to assess hypermobility and is included in Table 47.2. One point is given for each extremity with a

Table 47.2 Beighton criteria. Adapted from Beighton P, Horan F. Orthopaedic aspects of the Ehlers-Danlos syndrome. The Journal of Bone and Joint Surgery Br. 1969;51:444–453 [6]

Joint examination	Criteria for positive sign	Points
Passive hyperextension of small finger (each hand)	>90°	2
Passive thumb apposition to forearm (each thumb)	Thumb touches forearm	2
Elbow hyperextension (each elbow)	>10°	2
Knee hyperextension (each knee)	>10°	2
Trunk flexion with knees fully extended	Both palms flat on floor	1

Table 47.3 Criteria for diagnosis of classic EDS

Major criteria	Minor criteria	
1. Skin hyperextensibility and atrophic scarring	1. Easy bruising 2. Soft, doughy skin	5. Subcutaneous spheroids 6. Hernia
2. Joint hypermobility (Beighton score 5 or greater)	3. Skin fragility or splitting 4. Molluscoid pseudotumors	7. Epicanthal folds 8. First-degree relative

positive finding and one point for the trunk for a maximum of nine points. A total score of 5 or more indicates hypermobility. Additional physical findings associated with hypermobility include pes planovalgus, sulcus sign of the shoulder, swan-neck deformity of the fingers, and bunion deformity [6].

To establish the diagnosis of classic EDS, a patient must exhibit the major criterion of skin hyperextensibility with atrophic scarring plus either the second major criterion of joint hypermobility or three of the eight minor criteria. In patients meeting diagnostic criteria, molecular analysis of the COL5A1 and COL5A2 genes may be ordered to confirm the diagnosis of classical EDS. Diagnostic criteria for diagnosis of classic EDS are found in Table 47.3.

There are three clinical criteria for the diagnosis of hypermobile EDS: (1) generalized joint hypermobility; (2) a constellation of musculoskeletal complaints, systemic manifestations, and family history; and (3) exclusion of other possible disorders. Criteria 2 is quite complex and is described in more detail in Table 47.4. Patients must exhibit at least two of the three features below to satisfy these criteria [2].

Radiographs and other imaging modalities are not diagnostic for EDS and may appear normal in many cases. Nevertheless, radiographs can prove useful in the diagnosis and management of both acute and chronic musculoskeletal manifestations of EDS. When an acute joint dislocation is suspected, appropriate radiographic imaging should be obtained to confirm the diagnosis and rule out associated fractures. Joints with chronic, recurrent instability may show signs of bony hypoplasia, subluxation, and even degenerative changes.

Advanced modalities such as magnetic resonance imaging are not a routine part of the evaluation for EDS but may be employed to rule out ligamentous or intra-articular injury as part of the differential diagnosis in an acute injury. Magnetic

Table 47.4 Musculoskeletal complaints and systemic manifestations of hEDS

Feature A—systemic manifestations of connective tissue disorder (5 out of 12 must be present)	
1.	Unusually soft or velvety skin
2.	Mild skin hyperextensibility
3.	Unexplained striae such as striae distensae or rubrae at the back, groins, thighs, breasts, and/or abdomen in adolescents, men, or prepubertal women without a history of significant gain or loss of body fat or weight
4.	Bilateral piezogenic papules of the heel
5.	Recurrent or multiple abdominal hernia(s) (e.g., umbilical, inguinal, crural)
6.	Atrophic scarring involving at least two sites and without the formation of truly papyraceous and/or hemosideric scars as seen in classical EDS
7.	Pelvic floor, rectal, and/or uterine prolapse in children, men, or nulliparous women without a history of morbid obesity or other known predisposing medical condition
8.	Dental crowding and high or narrow palate
9.	Arachnodactyly, as defined in one or more of the following: (a) positive wrist sign (Steinberg sign) on both sides; (b) positive thumb sign (Walker sign) on both sides
10.	Arm span-to-height $\geq$1.05
11.	Mitral valve prolapse (MVP) mild or greater based on strict echocardiographic criteria
12.	Aortic root dilatation with Z-score >+2
Feature B—family history with at least one first-degree relative meeting the criteria for hEDS	
Feature C—musculoskeletal complications (at least one of three)	
1.	Musculoskeletal pain in two or more limbs, recurring daily for at least 3 months
2.	Chronic, widespread pain for $\geq$3 months
3.	Recurrent joint dislocations or frank joint instability
(a)	Three or more atraumatic dislocations in the same joint or two or more atraumatic dislocations in two different joints occurring at different times
(b)	Medical confirmation of joint instability at two or more sites not related to trauma

resonance arthrography of the shoulder often shows no apparent labral or ligamentous injury, even in highly unstable shoulders, but distension of the joint with intra-articular contrast may demonstrate a patulous joint capsule and lax glenohumeral ligaments.

Although it is not diagnostic for EDS, an echocardiogram should be performed in all patients being evaluated for hypermobility syndromes to rule out valve dysfunction, aortic root dilation, and other cardiac involvement. Annual echocardiograms may be recommended based on the subtype of EDS and findings on the initial study.

Treatment

Although musculoskeletal complaints may predominate in early childhood, the potential for multiple-organ system involvement, along with compounding psychosocial and emotional factors, mandates a multidisciplinary approach to patients with

EDS. Providers from cardiology, gastroenterology, genetics, internal medicine, ophthalmology, orthopedic surgery, orthotics, pain management, physiatry/rehabilitative medicine, psychiatry/psychology, and rheumatology, among others, may have an active role in the management of EDS.

Early physical and occupational therapy for children with hypotonia and developmental delay is important to promote the development of gross and fine motor skills. A continuing therapeutic exercise program emphasizing balance, proprioception, posture, and dynamic joint stabilization may help to improve muscle bulk, joint stability, and overall function [7].

Acute and chronic joint instability is common in the young patient with EDS. Acute injuries should be managed with prompt reduction of any dislocation followed by appropriate immobilization and rehabilitation. The RICE acronym (rest, ice, compression, elevation) for symptomatic management is always appropriate.

Orthoses may be used as an adjunct to improve joint stability and function. Finger-ring splints and orthoses of the foot, ankle, and knee may be useful for finger deformities, pes planovalgus, ankle instability, and patellar instability, respectively. The limitations of orthotics in preventing joint dislocations must be recognized, however, and they should not be considered a substitute for a therapeutic exercise program. Certain types of braces may restrict motion, thereby reducing pain, but may also lead to disuse and atrophy of surrounding muscle groups, further compromising their function.

Surgical stabilization may be an option to treat chronic joint instability, but nonoperative modalities should be exhausted prior to considering surgery. Wound healing, postoperative pain management, and surgical failure due to recurrent laxity are challenges to the success of surgical treatments. An attempt at nonoperative management is also indicated in congenital hip dislocations, congenital clubfeet, and kyphoscoliosis, but surgery may be necessary to obtain and maintain reduction of a dislocated hip, correct clubfoot deformity, or stabilize progressive spinal curvature.

Pain management presents many difficulties in the EDS patient. Medications do not improve the function of the affected soft tissues and may have side effects that paradoxically increase the risk of injury and chronic pain. Due to the higher incidence of gastrointestinal issues in EDS patients and the potential for chronic use, nonsteroidal anti-inflammatories should be prescribed with caution and may require co-administration with gastro-protective medications. In addition to the risk of addiction, chronic opioid use may cause central depression of muscle function and central sensitization, thereby increasing the risk of injury and heightening the perception of pain. Consultation with a multidisciplinary pain management clinic may be helpful to maximize non-pharmacological pain management modalities [8].

Lastly, the psychosocial impact on both the patient and family due to chronic pain, poor functional status, and disruption from frequent care episodes can be quite significant. Consultation with mental health professionals and social work is invaluable in the management of these complex issues.

Clinical Vignettes/Pearls

EDS is a chronic genetic disease that is often associated with poor function and chronic pain. As such, it can be a frustrating condition for patients, families, and providers. The key to minimizing these frustrations lies in making a prompt diagnosis, setting rational expectations regarding physical function, and proactively intervening to improve and maintain function. Hypotonia, developmental delay, and repetitive joint injury in the young child should alert the provider to the possibility of EDS. Providers should be aware of potential comorbidities including gastrointestinal complaints, cardiac involvement, dysautonomia, chronic pain, anxiety, and depression.

Natural History

Three distinct phases have been described in the natural history of EDS: hypermobility, pain, and stiffness. The "hypermobility" phase is most prevalent during childhood and is marked by the propensity for joint sprains and dislocations. The "pain" phase begins in the second to fourth decades of life with the establishment of progressive, often generalized, musculoskeletal pain, which can sometimes be mistaken for fibromyalgia or other pain disorders. Additional manifestations of chronic pain may develop including paresthesia, headache, pelvic pain/dysfunction, orthostatic intolerance, and gastrointestinal disorders. The "stiffness" phase develops late in life and likely results from progressive degenerative changes due to chronic joint injury. Mobility and function may be severely impaired [9].

Physical and psychosocial development can be impacted on many different levels in children with hypermobility. Joint laxity has been associated with impairments in proprioception, motor development, and physical fitness that ultimately decrease physical function. Increased pain intensity and psychological distress have also been reported in affected children with a decrease in the overall quality of life including both physical and emotional function [10].

Prevention

Because EDS is an inherited connective tissue disorder, prevention efforts are focused on early diagnosis of the disorder and on minimizing complications of hypermobility and associated soft-tissue fragility.

As previously mentioned, early intervention with appropriate physical and occupational therapy and continued participation in a therapeutic exercise program are critical to optimizing function and minimizing acute and chronic joint instability.

Educating patients and families with EDS about appropriate activities is also critical to minimize injury and optimize function. Chronic and repetitive injuries can cause patients to avoid activities due to fear of pain. Such avoidance behaviors may result in deconditioning that further compromises joint function, leading to a cycle of injury, pain, avoidance, and further deconditioning [11].

Children should avoid repetitive high-impact activities and excessive demonstrations of hypermobility. Although hypermobility may provide some relative advantages in activities such as swimming and ballet, repetitive supraphysiologic motions in such activities may increase the risk of overuse injury. Communication with school and coaches may be necessary to ensure that expectations of patient activity are appropriate and that modifications can be made according to the needs of the patient.

Skin should be protected from repetitive trauma with padding over pressure points as necessary. Traumatic and surgical wounds should be closed in multiple layers and with minimal tension to optimize wound healing. Dietary supplementation of ascorbic acid and protection from sun exposure are also recommended to maintain healthy skin.

Routine surveillance is an important facet of the long-term care of EDS. In addition to an initial evaluation, surveillance echocardiograms may be indicated based on initial findings and syndrome subtype. Screening for scoliosis should be performed during well-child visits, and patients with known scoliosis or kyphoscoliosis should be followed by an appropriate musculoskeletal specialist. Finally, mental health issues can have a profound impact on patients with EDS, and routine mental health screening should also be performed.

References

1. Parapia L, Jackson C. Ehlers-Danlos syndrome—a historical review. Br J Haematol. 2008;141(1):32–5.
2. Malfait F, Francomano C, Byers P, Belmont J, Berglund B, Black J, et al. The 2017 international classification of the Ehlers-Danlos syndromes. Am J Med Genet C Semin Med Genet. 2017;175(1):8–26.
3. Hakim AJ, Sahota A. Joint hypermobility and skin elasticity: the hereditary disorders of connective tissue. Clin Dermatol. 2006;24(6):521–33.
4. Tinkle B, Castori M, Berglund B, Cohen H, Grahame R, Kazkaz H, et al. Hypermobile Ehlers-Danlos syndrome (a.k.a. Ehlers-Danlos syndrome Type III and Ehlers-Danlos syndrome hypermobility type): clinical description and natural history. Am J Med Genet C Semin Med Genet. 2017;175(1):48–69.
5. Ghibellini G, Brancati F, Castori M. Neurodevelopmental attributes of joint hypermobility syndrome/Ehlers-Danlos syndrome, hypermobility type: update and perspectives. Am J Med Genet C Semin Med Genet. 2015;169C(1):107–16.
6. Beighton P, Horan F. Orthopaedic aspects of the Ehlers-Danlos syndrome. J Bone Joint Surg Br. 1969;51:444–53.
7. Engelbert RH, Juul-Kristensen B, Pacey V, de Wandele I, Smeenk S, Woinarosky N, et al. Evidence-based rationale for treatment of children, adolescents and adults with joint hypermobility syndrome/hypermobile EDS. Am J Med Genet. 2017;175C:158–67.

8. Ericson WB Jr, Wolman R. Orthopaedic management of the Ehlers-Danlos syndromes. Am J Med Genet C Semin Med Genet. 2017;175(1):188–94.
9. Castori M, Camerota F, Celletti C, Danese C, Santilli V, Saraceni VM, et al. Natural history and manifestations of the hypermobility type Ehlers-Danlos syndrome: a pilot study on 21 patients. Am J Med Genet A. 2010;152A(3):556–64.
10. Scheper MC, Nicholson LL, Adams RD, Tofts L, Pacey V. The natural history of children with joint hypermobility syndrome and Ehlers-Danlos hypermobility type: a longitudinal cohort study. Rheumatology (Oxford). 2017;56(12):2073–83.
11. Scheper MC, de Vries JE, Verbunt J, Engelbert RH. Chronic pain in hypermobility syndrome and Ehlers-Danlos syndrome (hypermobility type): it is a challenge. J Pain Res. 2015;8:591–601.

Chapter 48
Klippel-Trenaunay-Weber Syndrome

Robert S. Quigley and Neal Huang

Brief Overview of Condition

Klippel-Trenaunay syndrome (KTS) is a condition classically described as a triad of limb overgrowth, varicosities, and a port-wine stain nevus [1]. Klippel-Trenaunay-Weber syndrome (KTWS) shares many of the same clinical findings in conjunction with spinal arteriovenous malformations [2]. Unfortunately, the nomenclature for these two syndromes has been the source of confusion [3, 4]. Lindenauer described KTWS under the name of Parkes-Weber syndrome [5], while others used KTWS in reference to the originally described KTS. In this chapter, we describe Klippel-Trenaunay-Weber syndrome synonymously as Klippel-Trenaunay syndrome. A multidisciplinary effort between dermatology, orthopedics, and vascular surgery is often necessary in managing these patients as they have a unique need for management of limb growth, skin manifestations, and venous malformations.

Background Including Epidemiology and Pathophysiology

French physicians who described KTS originally explained the triad of symptoms in 1900, and diagnosis has been primarily established as a clinical diagnosis with two of the three triad symptoms [1]. A relatively rare condition, the prevalence of KTWS has been described anywhere from 1 in 100,000 [6] to 1 in 192,000 [7].

R. S. Quigley (✉) · N. Huang
Department of Orthopedic Surgery, University of Tennessee College of Medicine Chattanooga, Chattanooga, TN, USA
e-mail: robert.quigley@erlanger.org

J. F. Sarwark, R. L. Carl (eds.), *Orthopaedics for the Newborn and Young Child*,
https://doi.org/10.1007/978-3-031-11136-5_48

Genetics and pathophysiology of this condition have been relatively unknown until the recent discovery of the PIK3CA (phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha) gene's relationship to KTWS and other vascular malformation and overgrowth syndromes (3a). Somatic mutations of PIK3CA have shown to cause vascular malformations and unifocal venous malformations [6, 8]. Genetic testing of patients with Klippel-Trenaunay-Weber syndrome has been found to have an amalgam of different somatic activating mutations of the PIK3CA [9–11]. With a promising genetic link for KTWS being elucidated, a relationship between other conditions with similar clinical presentations is becoming more evident. Other overgrowth syndromes such as CLOVE syndrome (congenital lipomatous overgrowth, vascular malformations, and epidermal nevi), MCAP (megalencephaly-capillary malformation), and FAH (fibroadipose hyperplasia) have all been found to have involvement of the PIK3CA gene as well; thus, these conditions are grouped together under the PIK3CA-related overgrowth spectrum (PROS) description [11].

Clinical Presentation: History and Physical

Klippel-Trenaunay syndrome is rarely diagnosed at birth, and obvious signs of the syndrome such as obvious vascular lesions, visible lateral marginal vein, and lymphatic vesicles carry a worse prognosis in management. There is often no family history of KTS as this disease is typically caused by a sporadic somatic mutation. The port-wine stain noted at birth is the result of capillary malformation under the skin. This lesion is typically flat and can have anywhere from a pale pink color to a deep red. Other vascular lesions can be located in viscera such as the bladder, pelvis, retroperitoneal organs, gastrointestinal tract, and genitals. These vascular malformations, especially in the gastrointestinal tract, can lead to intestinal bleeding and anemia.

The hypertrophied limb can have severe length and girth discrepancies during growth when compared to the contralateral extremity and often lead to functional impairment [12]. Limb discrepancy is commonly due to underlying soft-tissue growth as well as long-bone hypertrophy. The majority of this growth occurs in childhood and stabilizes during early adulthood [13]. In a case series of 252 patients with KTS done by Jacob et al., they found that 98% of patients had port-wine stain, 72% had varicosities or venous malformations, 67% had limb hypertrophy, 63% had all three features [13]. Varicosities have a tendency to appear on the lateral portions of limbs, and the patient will often complain of swelling and pain due to vascular congestion [14].

The most salient points in examining a KTS patient are evaluating hands, feet, and spine curvature; measuring leg length discrepancies; and evaluating hypertrophied limb for vascular malformations via palpation and auscultation for bruits. KTS patients are noted to have had concomitant orthopedic conditions including digital anomalies of the hands and feet, metatarsus adductus, congenital clubfoot, and scoliosis [15–17].

Evaluation

Diagnosis of Klippel-Trenaunay syndrome is still made clinically. Despite new discoveries of its connection with the PIK3CA gene, identification of a mutation is not a diagnostic currently. Standing length X-rays can be used to evaluate long bone growth of the lower extremities, and plain films can be used for upper extremity long bones. Vascular malformations can be evaluated by duplex ultrasound imaging to assess the vascular anatomy and function [18]. MRI can be considered for evaluation of soft tissue, muscle, joint, and bones in the setting of overgrowth and vascular malformations. Studies can be obtained with gadolinium contrast and can help separate venous from arterial malformations, which can be helpful in clinical diagnosis, prognosis, and surgical planning. Contrast CT scans with venous-phase protocols can be used for preoperative planning as well but are considered inferior to MRI due to radiation exposure and renal toxicity of contrast. Ascending venography can be used if vascular surgery is being considered for superficial vein removal such as with ablation, sclerotherapy, ligation, or stripping [14].

Essential studies to order for a patient with suspected or diagnosed KTS are X-rays or joint survey films, MRI of affected limb and adjacent thorax, CBC, and coagulation labs.

Management

Treatment of KT syndrome remains largely symptomatic. Issues arising from KT syndrome that require treatment revolve around pain, varicosities, soft-tissue hypertrophy, and skeletal overgrowth of the affected limb. Because these issues cross specialty borders, a multidisciplinary approach is often best for these patients. The physician team typically consists of personnel from pediatrics, vascular surgery, plastic surgery, and orthopedic surgery. Other specialties include radiology, physical medicine and rehabilitation, pain management, and dermatology [19].

Pain is a common complaint in KTS. Pain may come from many sources, including chronic venous insufficiency, cellulitis, growing pains, thrombophlebitis, DVT, intraosseous bone malformations, calcified or scarred vascular malformations, arthritis, and neuropathic pain.

For varicosities and venous insufficiency, the mainstay of treatment is external compression via elastic or nonelastic garments. Prior to treatment of this condition, especially operative intervention, make sure to evaluate for competency of the deep venous system, since external compression or procedures are likely to fail if the deep venous system is incompetent. In addition to compression, elevating the extremity while in bed and also often during the day can help relieve the pain and swelling. Asymptomatic patients are treated nonoperatively because of the high recurrence rate of varicosities, which is close to 50% [20]. If nonoperative measures fail, procedures include surgery, sclerotherapy, and endovascular laser ablation. A common treatment for this is stripping of the veins and avulsion or excision of varicosities and vascular malformations [21]. Despite a 50% recurrence rate, patients report subjective and objective clinical improvement after surgery [20].

Limb hypertrophy can lead to limb length discrepancy and overgrowth of the foot involved. Shoe lift or custom shoes can be used when necessary. Overgrowth and limb length discrepancy in KTS can be unpredictable. This makes periodic clinical exam and full-length X-rays of the bilateral lower extremities necessary. A leg length discrepancy of over 2 cm is usually treated with surgery. For a skeletally immature patient, a properly timed epiphysiodesis is the best treatment [22]. If the patient is skeletally mature or if the leg length discrepancy is greater than 5 cm, a lengthening procedure may be considered. Soft-tissue or bony reduction procedures are used occasionally for the treatment of local gigantism. This can be used to help fit a foot into shoes or help with appearance [23]. Wound healing in KTS has been shown not to be a significant issue when operating on these patients [24].

Occasionally, patients will get intra-articular vascular malformations, causing knee flexion contractures. This can be treated with synovectomy and manipulation or, in extreme cases, amputation. Amputation can be complicated by bleeding, wound dehiscence, or infection [24]. Amputation may also be entertained for severe deformity, a large leg length discrepancy, or poor foot function.

Clinical Vignette

Patient is a 12-year-old male who first presented to an orthopedic surgeon at age 9 with low back pain, left lower extremity pain, and discoloration over the left side of his body. The pain in is lower extremity was aching, worse with activities and

prolonged standing. On examination, the patient had a clinic leg length discrepancy with left hemi-pelvis higher than the right. The patient had multiple port-wine stains only on the left side of his body involving the neck, the thorax, and the left lower extremity. The left calf circumference was increased on the left side. Left lower extremity had mild varicosities below the knee. No bruits were noted. Flexible flat-foot was present as well. Normal strength and sensation were observed. Radiographs were obtained of the bilateral lower extremities, showing a leg length discrepancy of 1.7 cm. The patient was given a prescription for a shoe lift, and counseling on activities was given. He became involved heavily with swimming, because it improved his leg pain. Sports on land made the pain worse. Over time, his leg length discrepancy progressed to 2.5 cm. The patient underwent an epiphysiodesis of the left distal femur and proximal tibia. At the latest follow-up, the patient's leg length discrepancy has improved to 1.5 cm with mild valgus deformity (Figs. 48.1, 48.2, 48.3, 48.4, and 48.5).

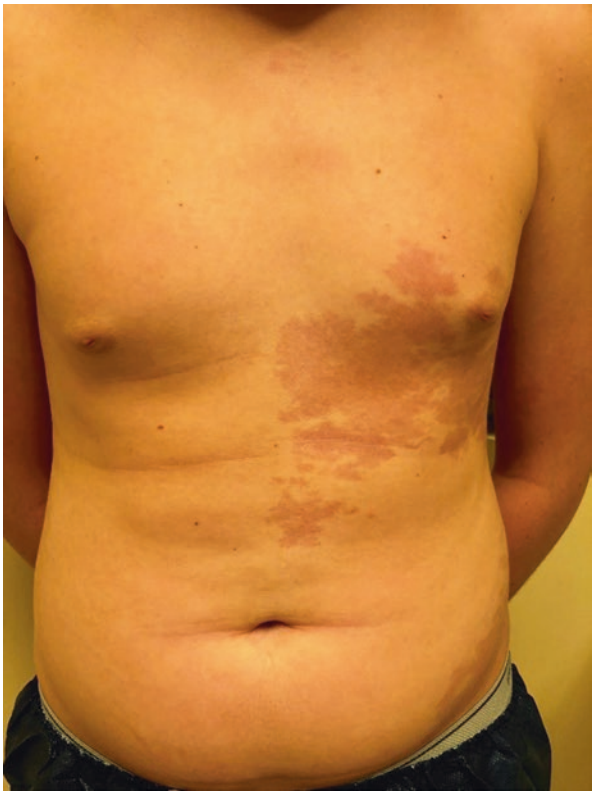


Fig. 48.1 Port-wine stain on the affected side of body

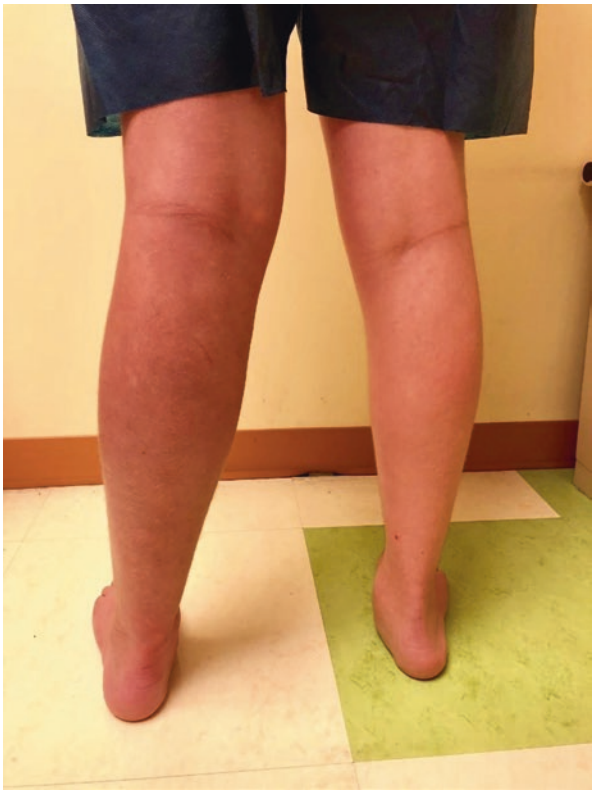


Fig. 48.2 Lower extremity hypertrophy with nevus present

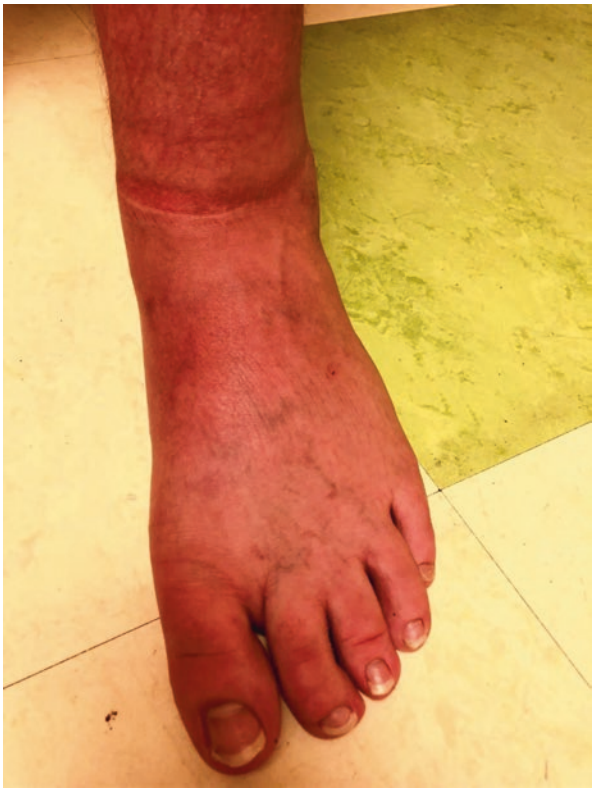


Fig. 48.3 Varicosities of the foot

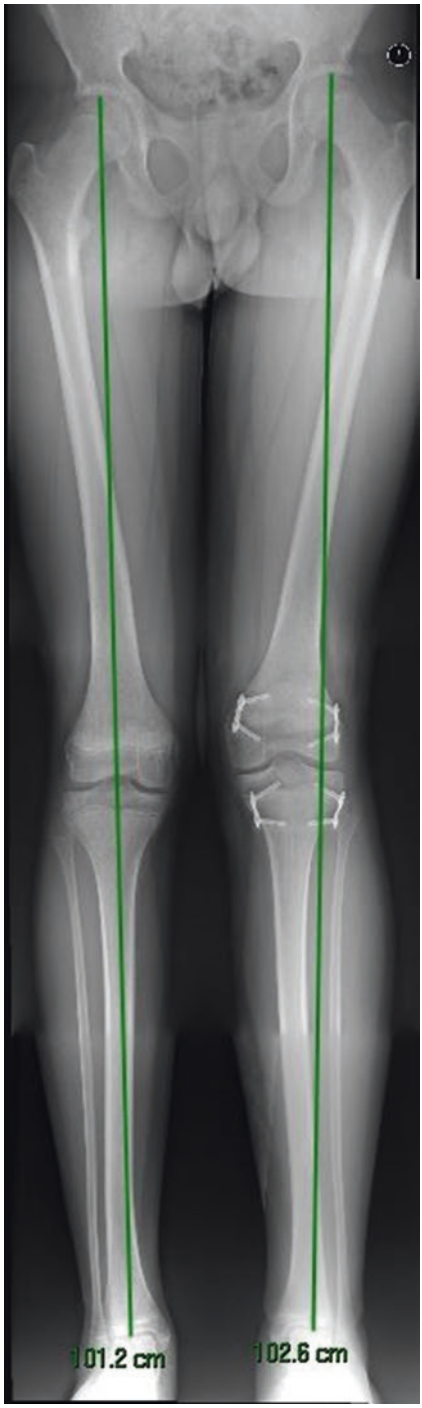


Fig. 48.4 Leg length discrepancy improving after epiphysiodesis

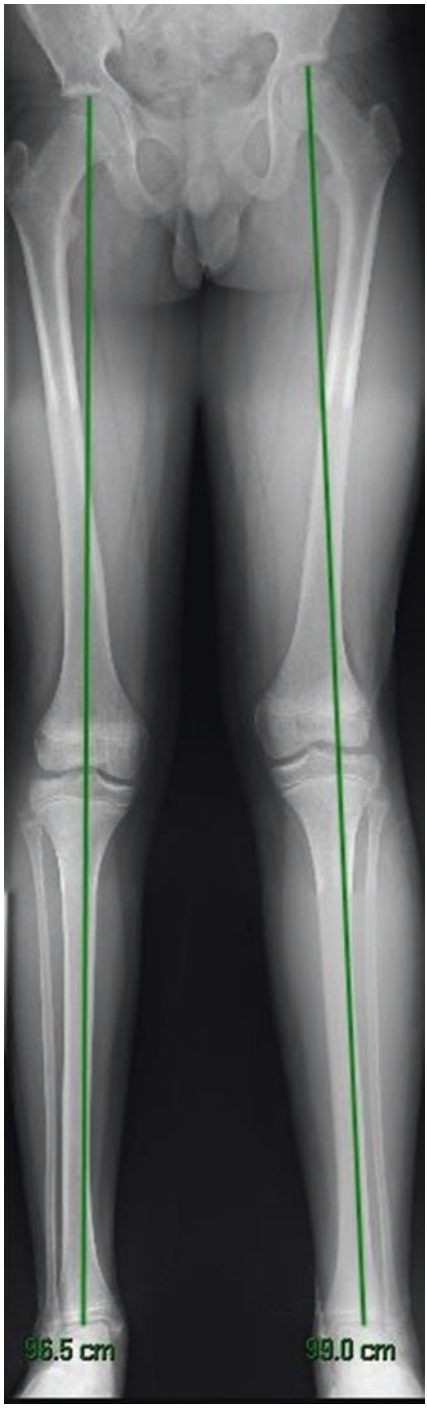


Fig. 48.5 Leg length discrepancy prior to surgery

Natural History, Primary and Secondary Prevention

The natural history of patients with KTS is largely unknown. There is a broad spectrum of severity affecting a number of different symptoms. Some patients have minimal hypertrophy with mild varicosities. Others sustain life-threatening complications. Numerous complications are associated with this syndrome, including thrombosis, coagulopathy, pulmonary embolism, heart failure, hemothorax, and bleeding from abnormal vessels of the gastrointestinal tract, kidney, or genitalia [20, 21]. Patients with abnormal lymphatic drainage are at a higher risk of contracting cellulitis and bacteremia [25]. Moreover, affected individuals may experience deep emotional and psychological trauma due to their deformed appearance [26]. Current research seems to suggest that KTS occurs sporadically and accidentally [19]. This makes primary prevention in KTS difficult. Many retrospective studies have been performed, but none have provided any prospective guidance. This limits the amount of secondary prevention that clinicians can provide [27, 28]. For instance, compression garments are used frequently in KTS patients. However, we have no long-term data looking at compression garment use in small children and whether or not its use early in life will help lead to fewer complications as adults. More prospective research needs to be done in order to provide insight into natural history and primary and secondary prevention in KTS patients.

References

1. Klippel M, Trenaunay P. Du noevus variqueux osteohypertrophique. Arch Gen Med. 1900;184(641).
2. Alomari A, Orbach D, Mulliken J, Bisdorff A, Fishman S, Norbash A, et al. Klippel-Trenaunay syndrome and spinal arteriovenous malformations: an erroneous association. Am J Neuroradiol. 2010;31(9):1608–12.
3. Weber FP. Angioma-formation in connection with hypertrophy of limbs and hemi-hypertrophy. Br J Dermatol. 1907;19(231).
4. Weber FP. Hemangiectatic hypertrophy of limbs—congenital phlebarteriectasis and so-called congenital varicose veins. Br J Childrens Dis. 1918;25(13).
5. Lindenauer SM. The Klippel-Trenaunay syndrome. Ann Surg. 1965;162(2):303–14.
6. Limaye N, Kangas J, Mendola A, Godfraind C, Schlögel MJ, Helaers R, et al. Somatic activating PIK3CA mutations cause venous malformation. Am J Human Genet. 2015;97(6):914–21.
7. Dimopoulos A, Sicko RJ, Kay DM, Rigler SL, Fan R, Romitti PA, et al. Copy number variants in a population-based investigation of Klippel-Trenaunay syndrome. Am J Med Genet Part A. 2016;173(2):352–9.
8. Blasio LD, Puliafito A, Gagliardi PA, Comunanza V, Somale D, Chiaverina G, et al. PI3K/mTOR inhibition promotes the regression of experimental vascular malformations driven by PIK3CA-activating mutations. Cell Death Dis. 2018;9(2).
9. Yeung KS, Ip JJ, Chow CP, Kuong EY, Tam PK, Chan GC, et al. Somatic PIK3CA mutations in seven patients with PIK3CA-related overgrowth spectrum. Am J Med Genet Part A. 2017;173(4):978–84.
10. Vahidnezhad H, Youssefian L, Uitto J. Klippel-Trenaunay syndrome belongs to the PIK3CA-related overgrowth spectrum (PROS). Exp Dermatol. 2015;25(1):17–9.

11. Luks VL, Kamitaki N, Vivero MP, Uller W, Rab R, Bovée JV, et al. Lymphatic and other vascular malformative/overgrowth disorders are caused by somatic mutations in PIK3CA. J Pediatr. 2015;166(4).
12. Enjolras O, Chapot R, Merland JJ. Vascular anomalies and the growth of limbs: a review. J Pediatr Orthopaed B. 2004;13(6):349–57.
13. Kihiczak GG, Meine JG, Schwartz RA, Janniger CK. Klippel–Trenaunay syndrome: a multisystem disorder possibly resulting from a pathogenic gene for vascular and tissue overgrowth. Int J Dermatol. 2006;45(8):883–90.
14. Wang SK, Drucker NA, Gupta AK, Marshalleck FE, Dalsing MC. Diagnosis and management of the venous malformations of Klippel-Trénaunay syndrome. J Vasc Surg Venous Lymphat Disord. 2017;5(4):587–95.
15. Jacob AG, Driscoll DJ, Shaughnessy WJ, Stanson AW, Clay RP, Gloviczki P. Klippel-Trenaunay syndrome: spectrum and management. Mayo Clin Proc. 1998;73(1):28–36.
16. Mcgrory BJ, Amadio PC, Dobyns JH. Anomalies of the fingers and toes associated with Klippel-Trenaunay syndrome. J Pediatr Orthopaed. 1992;12(3):419.
17. Mcgrory BJ, Amadio PC. Klippel-Trenaunay syndrome. J Pediatr Orthopaed. 1993;13(4):558.
18. Howlett DC, Roebuck DJ, Frazer CK, Ayers B. The use of ultrasound in the venous assessment of lower limb Klippel-Trenaunay syndrome. Eur J Radiol. 1994;18(3):224–6.
19. Lee A. Evaluation and management of pain in patients with Klippel-Trenaunay syndrome: a review. Pediatrics. 2005;115(3):744–9.
20. Noel AA, Gloviczki P, Cherry KJ, Rooke TW, Stanson AW, Driscoll DJ. Surgical treatment of venous malformations in Klippel-Trenaunay syndrome. J Vasc Surg. 2000;32:840–7.
21. Samuel M, Spitz L. Klippel-Trenaunay syndrome: clinical features, complications and management in children. Br J Surg. 1995;82(6):757–61.
22. Guidera KJ, Brinker MR, Kousseff BG, Helal AA, Pugh LI, Ganey TM, et al. Overgrowth management in Klippel-Trenaunay-Weber and Proteus syndromes. J Pediatr Orthopaed. 1993;13(4):459–66.
23. Stringel G, Dastous J. Klippel-Trenaunay syndrome and other cases of lower limb hypertrophy. J Pediatr Orthopaed. 1988;8(1):123.
24. Gates PE, Drvaric DM, Kruger L. Wound healing in orthopaedic procedures for Klippel-Trenaunay syndrome. J Pediatr Orthopaed. 1996;16(6):723–6.
25. Bird LM, Jones MC, Kuppermann N, et al. Gram-negative bacteremia in four patients with Klippel-Trenaunay-Weber syndrome. Pediatrics. 1996;97:739–41.
26. van der Ploeg HM, Ploeg MNVD, Ploeg-Stapert JDVD. Psychological aspects of the Klippel-Trenaunay syndrome. J Psychosom Res. 1995;39(2):183–91.
27. Telander RL, Kaufman BH, Gloviczki P, et al. Prognosis and management of lesions of the trunk in children with Klippel-Trenaunay syndrome. J Pediatr Surg. 1984;19:417–22.
28. Sung HM, Chung HY, Lee SJ, Lee JM, Huh S, Lee JW, Choi KY, Yang JD, Cho BC. Clinical experience of the Klippel-Trenaunay syndrome. Arch Plast Surg. 2015;42(5):552–8.

Chapter 49
Neurofibromatosis

Sina Malekian

Brief Overview

Neurofibromatosis (NF) is a genetic disorder that, among other complications, causes tumors to grow in the nervous system. These tumors sometimes become malignant, but most often are benign. There are three types of NF, each presenting with different signs and symptoms, known as neurofibromatosis type 1 (NF1), neurofibromatosis type 2 (NF2), and schwannomatosis. NF1 is the most common and the only type of NF found to be associated with skeletal disorders. NF1 is generally characterized by neurofibromas (benign tumors) and dermal features such as café-au-lait macules and skinfold freckling. NF2 is characterized by bilateral vestibular schwannomas (benign tumors in both ears), which can cause hearing and balancing complications. Schwannomatosis is characterized by tumors developing on the cranial, spinal, and peripheral nerves, but rarely on the auditory nerve. Due to skeletal complications unique to NF1 and not to NF2 and schwannomatosis, NF1 and its associated orthopedic manifestations will be the focus of this chapter. Non-orthopedic presentations of NF1 will also briefly be discussed.

Epidemiology and Pathophysiology

NF1 is an autosomal dominant genetic disorder that has an incidence at birth of approximately 1 in 3000 worldwide [1]. About half of NF1 cases are inherited, and the other half are the result of de novo (sporadic) mutation [2, 3]. When functional,

S. Malekian (✉)
Department of Orthopaedic Surgery, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA
e-mail: smalekian@luriechildrens.org

J. F. Sarwark, R. L. Carl (eds.), *Orthopaedics for the Newborn and Young Child*,
https://doi.org/10.1007/978-3-031-11136-5_49

the *NF1* gene produces neurofibromin, a protein with tumor-suppressing properties [4] expressed widely in human tissue including neurons, glial cells, immune cells, and cells of the adrenal medulla [5]. NF1 is caused by loss-of-function mutations in the *NF1* gene, resulting in the production of nonfunctional neurofibromin [6] and consequently increased risk of developing tumors in affected individuals [7]. Almost all people with NF1 develop neurofibromas, which are benign nerve sheath tumors developing in spinal, peripheral, or cranial nerves [5].

The life expectancy of those with NF1 has been observed to be 8–15 years less than the general population, with estimates as great as 26 years less in women [8, 9]. The most common observed cause of death in individuals with NF1 is malignant tumors. Malignant peripheral nerve sheath tumors (MPNSTs) are the most common NF1-associated malignancies, with an estimated risk of affecting 20–39% of those less than 50 years of age and a lifetime risk of ~60% [5, 10]. The 5-year survival rate for NF1 patients with MPNST is 21% (median 1.3 years) [11]. Other potential cancers associated with NF1 include, but are not limited to, brain tumors, endocrine cancers, connective tissue malignancies, and leukemia in children [5].

Bone defects observed in NF1 patients have been attributed to the loss of both copies of NF1 in osteoclasts and/or osteoblasts, resulting in reduced bone mineral density and higher risk of fracture [5]. Bone mineral density appears even more reduced in NF1 patients with scoliosis that require surgical treatment [12]. Scoliosis, the most common skeletal defect among NF1 patients, is observed in up to 30% of afflicted individuals. Congenital pseudarthrosis of the tibia (CPT) is also a common orthopedic manifestation for NF1 patients, affecting 2–5% of individuals [5, 13]. Although CPT is relatively uncommon in the general population—observed in 1 in 250,000 births—75% of individuals with CPT have NF1 [14].

Other common features of NF1 include café-au-lait macules, prevalent in 99% of patients by age 1 year [14]; skinfold freckling, appearing in 90% of individuals [14]; optic pathway gliomas (OPGs), occurring in 15–20% of children, and visual deficits in less than half of these individuals, with prevalence declining to less than 5% in adults [15]; Lisch nodules, presenting in >70% of children by age 10 years [16]; and cognitive impairment, presenting in ~80% of children [5].

Clinical Presentations

Common clinical presentations of NF1 are included in the diagnostic criteria set by the National Institute of Health (NIH) Consensus Development Conference of 1987 [17], which states that diagnostic criteria are met when two or more of the following are found in an individual:

- Six or more café-au-lait macules (Fig. 49.1) over 5 mm in greatest diameter in prepubertal individuals and over 15 mm in greatest diameter in postpubertal individuals
- Two or more neurofibromas of any type or one plexiform neurofibroma

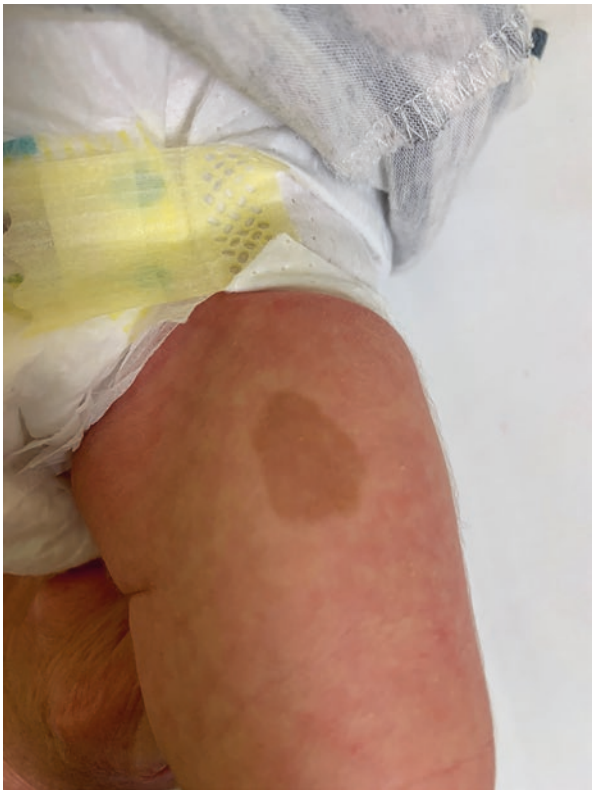


Fig. 49.1 Café au lait spot in a young infant. Image courtesy of Rebecca L. Carl, MD

- Freckling in the axillary or inguinal region
- Optic glioma
- Two or more Lisch nodules (iris hamartomas)
- A distinctive osseous lesion such as sphenoid dysplasia or thinning of long bone cortex with or without pseudarthrosis
- A first-degree relative (parent, sibling, or offspring) with NF1 by the above criteria

Orthopedic Manifestations

Scoliosis can develop in one of the two forms: dystrophic or non-dystrophic. Clinical and radiological features of non-dystrophic scoliosis are less pronounced than dystrophic scoliosis and closely resemble adolescent idiopathic scoliosis (AIS); however, non-dystrophic scoliosis has an earlier onset and poorer prognosis than AIS [14]. Non-dystrophic scoliosis usually involves 8–10 spinal segments and tends to present in older children relative to the younger age of onset for dystrophic scoliosis [18].

Dystrophic (degenerative) scoliosis typically involves 4–6 sharply angulated segments that cause distortion of the vertebral bodies and ribs [7]. Dystrophic scoliosis is thought to be caused by bony dysplasia or intraspinal pathology, including common features of rib penciling, vertebral scalloping, dumbbell lesions, and dural ectasia [14, 19]. Less common dystrophic features include spindling of the transverse process, vertebral wedging and rotation, foraminal enlargement, and defective pedicles [14, 20]. Dystrophic curves can be classified into type I and type II curves. In addition to scoliosis in the coronal plane, type I curves exhibit kyphosis in the sagittal plane measuring <50°, while type II curves exhibit kyphosis measuring >50° [14, 21]. In severe cases, dystrophic scoliosis can present with respiratory problems as made evident by disturbed sleep and excessive snoring [7].

Along with spinal deformities, common orthopedic manifestations of NF1 include congenital pseudarthrosis of the tibia (CPT), decreased bone mass, and sphenoid wing dysplasia. Tibial dysplasia is characterized by congenital bowing, which often produces a visible deformity, and it is apparent in the first few months of life [5, 7]. This congenital bowing can result in a fracture, which subsequently can lead to pseudarthrosis, or a false joint, due to failure of primary union at the fracture site [5]. Sphenoid wing dysplasia typically presents as a unilateral defect affecting the orbital plate and frontal lobe, which is usually seen when one eye appears asymmetric, proptotic, or sunken [13].

Skin Manifestations

Café-au-lait macules commonly emerge by age 1 year [14]. These lesions appear as flat, coffee-colored areas of hyperpigmentation, oval or rounded in shape, with an average size of 2–5 cm [14] (Fig. 49.1). Skinfold freckling is displayed as small, brown macules typically emerging by age 7 years and is commonly found in the axillae, inguinal region, breast folds, neck, and upper eyelids [14]. Neither café-au-lait patches nor skinfold freckling cause complications other than potential distress to patients due to the appearance of these manifestations [7].

Lisch Nodules

Lisch nodules are pigmented hamartomas of the iris [14] usually developing before 10 years of age [16]. Lisch nodules generally present in the lower pole of the iris and appear as reddish-brown spots in blue or green eyes and hypopigmented spots in brown eyes [22]. They do not cause visual impairment [14].

Optic Pathway Gliomas (OPGs)

Optic gliomas (visual pathway tumors) are low-grade pilocytic astrocytomas of the optic nerve and/or optic chiasm [14]. Optic gliomas are generally benign, though there is a greater risk for symptomatic optic pathway gliomas to develop before the age of 6 years. Potential symptoms include impaired visual acuity, abnormal pupillary function, decreased color vision, optic atrophy, and proptosis [23].

Neurofibromas

Neurofibromas—benign peripheral nerve sheath tumors composed of Schwann cells, fibroblasts, perineural cells, and mast cells [14]—appear with a purplish tone and are found in most individuals with NF1, developing usually in the late teens or early 20s [7]. Subcutaneous neurofibromas grow just under the surface of the skin and are evident upon palpation [7]. They can be painful, itchy, disfiguring, or tender when touched [24].

Plexiform neurofibromas are composed of the same cell types as cutaneous neurofibromas but also include an extracellular matrix and vascular supply [14]. Plexiform neurofibromas cause significant morbidity as they are diffuse and grow along the length of a nerve, potentially involving nerve branches and plexus [7]. Bony hypertrophy is sometimes evident as plexiform neurofibromas infiltrate surrounding soft tissue [7]. Plexiform neurofibromas can cause pain, numbness, weakness, and disfigurement [24].

Malignant Peripheral Nerve Sheath Tumors (MPNSTs)

MPNSTs are often difficult to detect and usually arise from malignant transformations of preexisting plexiform neurofibromas predominantly in individuals aged 20–35 years [7]. MPNSTs are identified clinically upon sudden onset of pain at the affected area, enlargement, and new neurologic deficits [14].

Testing and Evaluation

NF1 can usually be diagnosed upon an assessment of family history and a physical examination for the clinical features presented by the aforementioned NIH Consensus Development Conference diagnostic criteria. Although one study found

that nearly all (97%) NF1 patients meet the criteria for diagnosis by 8 years of age [16], signs and symptoms of NF1 do not always present earlier in childhood (<6 years of age), often resulting in delayed diagnosis [5]. Café-au-lait macules, the most commonly identified feature of NF1, are observed in the general population and in other disorders. This can make diagnosis especially challenging for children without a family history and who present only with café-au-lait macules.

Genetic testing may be appropriate in scenarios where NF1 features are difficult to differentiate from other disorders with similar clinical presentations, such as Legius syndrome [5]. Legius syndrome has early life manifestations similar to NF1, including café-au-lait macules and freckling in the armpits and groin [25]. Genetic testing can also differentiate a diagnosis of NF1 from diagnosing skin hyperpigmentation, mismatch repair and overgrowth syndromes, and misidentified neurofibromas [5]. As NF1 is an autosomal dominant disorder, prenatal genetic testing can be carried out when the *NF1* mutation is found in a parent. Prenatal genetic testing cannot, however, predict the severity of NF1 symptoms [5, 26].

Imaging characteristics of NF1 and related orthopedic manifestations are important to understand when evaluating patients with this disorder. Non-dystrophic scoliosis presents similarly to adolescent idiopathic scoliosis but with an earlier onset [14]. Dystrophic scoliosis usually presents with 4–6 sharply angulated segments and progresses more rapidly with a poorer prognosis than non-dystrophic cases [14]. Dural ectasia is the circumferential dilation of the dural sac and often presents with vertebral scalloping [27, 28]. Vertebral scalloping usually develops in the concavity of the scoliotic curve or at levels unrelated to the curve, and it is diagnosed when the depth of scalloping is >3 mm in the thoracic vertebrae and/or >4 mm in the lumbar vertebrae [27, 28]. Rib penciling—when the rib is narrower in diameter than the second rib—may resemble twisted ribbons [18]. Other skeletal imaging manifestations include cortical thinning, erosive defects, periosteal proliferation, sclerosis, and cystlike lesions [28].

Treatment and Management

Scoliosis

Currently, there is no complete treatment available for NF1. Clinical management typically involves surveillance and symptomatic treatment [5]. People with NF1 require early scoliosis screening, including MRI and/or CT scans to assess dystrophic features, rapidly progressing non-dystrophic features, and both intraspinal and paraspinal tumors [14]. The presence of paraspinal tumors should be ruled out prior to surgery due to limited surgical exposure and increased risk of bleeding [14].

For non-dystrophic scoliosis: curves <20° require observation; curves between 20° and 40° require bracing; and curves ≥40° require fusion. For less severe non-dystrophic curves, posterior instrumentation will suffice for successful treatment.

For curves ≥90°, anterior-posterior (AP) fusion is recommended [14, 29, 30]. Due to the rapidly progressing nature of dystrophic scoliosis, bracing has not been found to successfully prevent curve progression. Recommendations are made for early and aggressive surgical interventions for dystrophic curves, including curves between 20° and 40°. For dystrophic curves <20°, close monitoring of curve progression should be done in 6-month intervals [14, 21, 29–31].

Along with curves ≥90°, AP fusion is required for rapidly progressing dystrophic curves and when development of acute kyphosis is observed [14, 21]. Though posterior fusion with segmental spinal instrumentation has been shown to stabilize type I dystrophic curves, posterior instrumentation alone has a greater associated risk with pseudarthrosis than AP intervention [14, 30]. Posterior instrumentation alone also has poorer outcomes for the more severe type II curves as well, providing further justification for AP intervention [14, 29].

Instrumentation challenges, such as hardware dislodgement, are due to erosion and weakening of bony features [7, 14]. Dislodgment of hooks used for proximal fixation is particularly a concern for NF1 patients with osteoporosis and deformed posterior elements [14]. Pedicle screws offer better vertebral grip and stable fixation despite potentially weak and thin pedicles [14]. Titanium instrumentation is preferred to allow for postoperative MRI [14].

Congenital Pseudarthrosis of the Tibia (CPT)

Bracing for CPT can be used to prevent fracture in a dysplastic bone, to delay surgical intervention in a fractured dysplastic tibia, and to support good ambulatory function whether a fracture is present or not [14, 32, 33]. Ankle-foot orthosis is appropriate for a non-weight-bearing child presenting with anterolateral bowing. Once weight bearing begins, bracing should be switched to a knee-ankle-foot orthosis [14].

Surgical intervention—such as bone grafting with intramedullary fixation, external fixation, and free vascularized fibular grafting—is required for a fractured tibia in CPT patients as casting and bracing are not effective in achieving union [14]. The goal of surgical intervention is to maximize union and achieve stable fixation and correction of angular deformity [14]. Circular wire fixation following resection of the pseudarthrosis site can provide compression and stable fixation of the bone. External fixation can correct axial deviation and limb-length discrepancy while achieving union [14, 32].

Common concerns with managing CPT include risk of refracture, valgus deformity, malalignment, and limb-length discrepancy [14]. Studies have shown that leaving the intramedullary device in place after the bone has healed can help prevent refracture [14, 34]. Amputation after multiple failed attempts at surgery may be necessary in cases of severe limb-length discrepancies [14]. Risk factors associated with free vascularized fibular grafting include donor-site morbidity, failure of graft incorporation, development of ankle valgus, dorsiflexion weakness of the foot and ankle, and few remaining options for further reconstruction if union is not achieved [14].

Natural History and Prevention

A study by Durrani et al. [20] showed 81% of spinal deformities associated with NF1 that developed before the age of 7 years to exhibit modulation. Modulation, unique to spinal deformities in NF1, is the ability for the spinal deformity to transform and develop features of dystrophic scoliosis [20]. The possibility exists for non-dystrophic scoliosis to modulate into dystrophic scoliosis over time. Dystrophic scoliosis is less common than non-dystrophic but considered to be the more severe form as it is characterized by rapid progression, often despite treatment [14].

Modulation is different from progression as progression measures the severity of the curve, including measures of the increase in scoliosis and kyphosis [20]. Increased progression is anticipated if a patient under 7 years acquires at least three penciled ribs or a combination of three other dystrophic features [20]. Progression of dystrophic features is also associated with kyphoscoliosis with the possibility of complication from draping of the spinal cord or compression, which can lead to neurologic defects [14, 21].

CPT usually presents within the first year of life and is described as tibial dysplasia resulting in anterolateral bowing of the bone [35]. Anterolateral bowing can lead to tibial nonunion fractures followed by pseudarthrosis [14]. Tibial nonunion, tibial bowing, and reduced growth in the distal tibial epiphysis can also result in limb length discrepancy [35]. Bracing can be used both therapeutically and preventively for CPT.

Decreased bone mass can potentially predispose affected individuals to the development of osteoporosis and fracture [36]. Targeting interventions to improve bone strength in children with NF1 through weight-bearing activities, for example, can possibly help prevent skeletal problems later in life; however, more research in this area is needed to confirm potential benefits of weight-bearing activities in this patient population [36].

There is no definitive prevention of NF other than preclusion of passing the genetic disorder from a parent to a child. Prenatal genetic testing is possible to detect a mutation in the *NF1* gene. Genetic testing for NF2 is accurate in 65% of individuals tested, and genetic testing for schwannomatosis is not available [37].

References

1. Evans DG, Howard E, Giblin C, Clancy T, Spencer H, Huson SM, et al. Birth incidence and prevalence of tumor-prone syndromes: estimates from a UK family genetic register service. Am J Med Genet A. 2010;152a(2):327–32.
2. Jouhilahti E-M, Peltonen S, Heape AM, Peltonen J. The pathoetiology of neurofibromatosis 1. Am J Pathol. 2011;178(5):1932–9.
3. Friedman JM. Neurofibromatosis 1. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, LJH B, Stephens K, et al., editors. GeneReviews®. Seattle, WA: University of Washington, Seattle; 1993.

4. Ratner N, Miller SJ. A RASopathy gene commonly mutated in cancer: the neurofibromatosis type 1 tumour suppressor. Nat Rev Cancer. 2015;15(5):290–301.
5. Gutmann DH, Ferner RE, Listernick RH, Korf BR, Wolters PL, Johnson KJ. Neurofibromatosis type 1. Nat Rev Dis Primers. 2017;3:17004.
6. Esposito T, Piluso G, Saracino D, Uccello R, Schettino C, Dato C, et al. A novel diagnostic method to detect truncated neurofibromin in neurofibromatosis 1. J Neurochem. 2015;135(6):1123–8.
7. Ferner RE, Huson SM, Thomas N, Moss C, Willshaw H, Evans DG, et al. Guidelines for the diagnosis and management of individuals with neurofibromatosis 1. J Med Genet. 2007;44(2):81–8.
8. Evans DG, O'Hara C, Wilding A, Ingham SL, Howard E, Dawson J, et al. Mortality in neurofibromatosis 1: in North West England: an assessment of actuarial survival in a region of the UK since 1989. Eur J Human Genet. 2011;19(11):1187–91.
9. Uusitalo E, Leppavirta J, Koffert A, Suominen S, Vahtera J, Vahlberg T, et al. Incidence and mortality of neurofibromatosis: a total population study in Finland. J Invest Dermatol. 2015;135(3):904–6.
10. Uusitalo E, Rantanen M, Kallionpaa RA, Poyhonen M, Leppavirta J, Yla-Outinen H, et al. Distinctive cancer associations in patients with neurofibromatosis type 1. J Clin Oncol. 2016;34(17):1978–86.
11. Evans DG, Baser ME, McGaughran J, Sharif S, Howard E, Moran A. Malignant peripheral nerve sheath tumours in neurofibromatosis 1. J Med Genet. 2002;39(5):311–4.
12. Lammert M, Kappler M, Mautner VF, Lammert K, Storkel S, Friedman JM, et al. Decreased bone mineral density in patients with neurofibromatosis 1. Osteoporos Int. 2005;16(9):1161–6.
13. Hirbe AC, Gutmann DH. Neurofibromatosis type 1: a multidisciplinary approach to care. Lancet Neurol. 2014;13(8):834–43.
14. Feldman DS, Jordan C, Fonseca L. Orthopaedic manifestations of neurofibromatosis type 1. J Am Acad Orthop Surg. 2010;18(6):346–57.
15. de Blank PMK, Fisher MJ, Liu GT, Gutmann DH, Listernick R, Ferner RE, et al. Optic pathway gliomas in neurofibromatosis type 1: an update: surveillance, treatment indications, and biomarkers of vision. J Neuroophthalmol. 2017;37(Suppl 1):S23–s32.
16. DeBella K, Szudek J, Friedman JM. Use of the national institutes of health criteria for diagnosis of neurofibromatosis 1 in children. Pediatrics. 2000;105(3 Pt 1):608–14.
17. Neurofibromatosis. Conference statement. National Institutes of Health Consensus Development Conference. Arch Neurol. 1988;45(5):575–8.
18. Crawford AH. Orthopedic Manifestations of Neurofibromatosis Type 1 (von Recklinghausen Disease). 2018. https://emedicine.medscape.com/article/1260124-overview#a1.
19. Tsirikos AI, Saifuddin A, Noordeen MH. Spinal deformity in neurofibromatosis type-1: diagnosis and treatment. Eur Spine J. 2005;14(5):427–39.
20. Durrani AA, Crawford AH, Chouhdry SN, Saifuddin A, Morley TR. Modulation of spinal deformities in patients with neurofibromatosis type 1. Spine. 2000;25(1):69–75.
21. Parisini P, Di Silvestre M, Greggi T, Paderni S, Cervellati S, Savini R. Surgical correction of dystrophic spinal curves in neurofibromatosis. A review of 56 patients. Spine. 1999;24(21):2247–53.
22. Tonsgard JH. Clinical manifestations and management of neurofibromatosis type 1. Sem Pediatr Neurol. 2006;13(1):2–7.
23. Listernick R, Louis DN, Packer RJ, Gutmann DH. Optic pathway gliomas in children with neurofibromatosis 1: consensus statement from the NF1 Optic Pathway Glioma Task Force. Ann Neurol. 1997;41(2):143–9.
24. Johns Hopkins Medicine. Tumors associated with neurofibromatosis (NF) type 1. https://www.hopkinsmedicine.org/neurology_neurosurgery/centers_clinics/neurofibromatosis/nf1/tumors-nf1.html.
25. National Library of Medicine—Genetics Home Reference. Legius syndrome. 2011. https://ghr.nlm.nih.gov/condition/legius-syndrome#.

26. Verlinsky Y, Rechitsky S, Verlinsky O, Chistokhina A, Sharapova T, Masciangelo C, et al. Preimplantation diagnosis for neurofibromatosis. Reprod Biomed Online. 2002;4(3):218–22.
27. Tsirikos AI, Ramachandran M, Lee J, Saifuddin A. Assessment of vertebral scalloping in neurofibromatosis type 1 with plain radiography and MRI. Clin Radiol. 2004;59(11):1009–17.
28. Patel NB, Stacy GS. Musculoskeletal manifestations of neurofibromatosis type 1. Am J Roentgenol. 2012;199(1):W99–W106.
29. Li M, Fang X, Li Y, Ni J, Gu S, Zhu X. Successful use of posterior instrumented spinal fusion alone for scoliosis in 19 patients with neurofibromatosis type-1 followed up for at least 25 months. Arch Orthop Trauma Surg. 2009;129(7):915–21.
30. Halmai V, Doman I, de Jonge T, Illes T. Surgical treatment of spinal deformities associated with neurofibromatosis type 1. Report of 12 cases. J Neurosurg. 2002;97(3 Suppl):310–6.
31. Singh K, Samartzis D, An HS. Neurofibromatosis type I with severe dystrophic kyphoscoliosis and its operative management via a simultaneous anterior-posterior approach: a case report and review of the literature. Spine J. 2005;5(4):461–6.
32. Ohnishi I, Sato W, Matsuyama J, Yajima H, Haga N, Kamegaya M, et al. Treatment of congenital pseudarthrosis of the tibia: a multicenter study in Japan. J Pediatr Orthop. 2005;25(2):219–24.
33. Johnston CE. Congenital pseudarthrosis of the tibia. J Bone Joint Surg Am. 2002;84-A:1799–810.
34. Dobbs MB, Rich MM, Gordon JE, Szymanski DA, Schoenecker PL. Use of an intramedullary rod for treatment of congenital pseudarthrosis of the tibia. A long-term follow-up study. J Bone Joint Surg Am. 2004;86-a(6):1186–97.
35. Shah H, Rousset M, Canavese F. Congenital pseudarthrosis of the tibia: management and complications. Indian J Orthop. 2012;46(6):616–26.
36. Stevenson DA, Moyer-Mileur LJ, Murray M, Slater H, Sheng X, Carey JC, et al. Bone mineral density in children and adolescents with neurofibromatosis type 1. J Pediatr. 2007;150(1):83–8.
37. National Library of Medicine—Genetics Home Reference. Neurofibromatosis type 1. 2012. https://ghr.nlm.nih.gov/condition/neurofibromatosis-type-1.

Chapter 50
Marfan Syndrome

Merritt E. Adams

Marfan Syndrome Overview

Marfan syndrome (MFS) is one of the most common inherited connective tissue disorders. It was first described in 1896 in a 5.5-year-old female patient. The incidence of Marfan syndrome is anywhere from 1 in 3000 to 1 in 5000. It is one of the most commonly inherited connective tissue disorders [1]. Marfan syndrome tends to be inherited in an autosomal dominant manner, but there have been reports of a de novo mutation in 25% of cases and even rarer in an autosomal recessive disorder [2]. It does not appear to have any male/female predominance nor have any ethnicity predominance. Due to the variability of the disease at times, the presenting symptom can be sudden death as a result of cardiac manifestations. This variability may be due to the fact that more than 2500 mutations have been identified through the FBN1, while missense mutations still make up the most common type [1]. The diagnosis is made using the Ghent criteria, which were revised in 2010; this places more emphasis on the cardinal features of Marfan syndrome: including aortic root dilatation and ectopia lentis and less emphasis on other features such as joint hypermobility, which is shared with other syndromes [3].

Fibrillin-1 protein is an important matrix component of both elastic and nonelastic tissues; it is the main constituent protein of extracellular microfibrils that are thought to contribute to the formation and maintenance of elastic fibers [4, 5]. How this translates to disease is not well known. The majority of people with Marfan syndrome have visible signs of the syndrome including tall slender stature, dolichostenomelia, arachnodactyly, pectus excavatum/pectus carinatum chest deformities, and scoliosis [1] (Fig. 50.1). Most affected individuals will have rapidly progressive

M. E. Adams (✉)
Department of Orthopedic Surgery, Children's Hospital at Erlanger, UT College of Medicine Chattanooga, Chattanooga, TN, USA
e-mail: merritt.adams@erlanger.org

J. F. Sarwark, R. L. Carl (eds.), *Orthopaedics for the Newborn and Young Child*,
https://doi.org/10.1007/978-3-031-11136-5_50

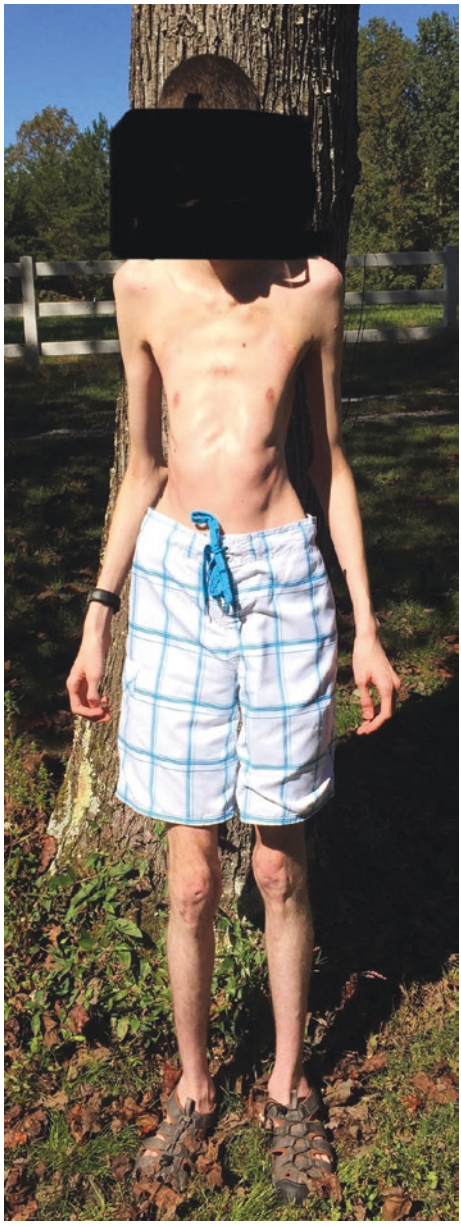


Fig. 50.1 Teenage boy with Marfan syndrome; note the tall, skinny stature, long arms, and arachnodactyly. There is also a pectus deformity

myopia, and approximately 60% will have ectopia lentis. The major cause of morbidity and mortality for Marfan syndrome stems from the cardiovascular disease. The main cardiac feature is aortic root disease, leading to aneurysms, aortic regurgitation, and dissection [6]. Other cardiac features include mitral valve prolapse and

mitral regurgitation. Dural ectasia is a major criterion for diagnosis, and other features associated with Marfan syndrome include spontaneous pneumothorax, recurrent hernia, and striae atrophicae. An infantile form of Marfan syndrome also exists. This condition is associated with skeletal features, mitral valve prolapse and regurgitation, and aortic root dilatation [7].

The diagnosis of Marfan syndrome should be considered in any patient presenting with any of the above symptoms, especially given its variability. A referral should be made to cardiology and genetics, but its approach to treatment should be multidisciplinary, which should also include an ophthalmologist, orthopedist, and cardiothoracic surgeon. Oftentimes, genetics is not as widely available as other specialties. The diagnosis is made using the modified Ghent criteria as well as with genetic testing. The Ghent criteria were originally proposed in 1996 and revised in 2010. The revision emphasizes cardiovascular manifestations, in which aortic root aneurysm and ectopia lentis are considered cardinal clinical features. In the absence of any family history, the presence of those two manifestations is sufficient for the unequivocal diagnosis of MFS. In the absence of either of those two features, the presence of an FBN1 mutation or a combination of systemic manifestations is required, for which there is a revised scoring system. FBN1 testing is not mandatory but carries greater weight in the diagnostic assessment [3]. The advances of genetic testing have helped confirm the diagnosis and are included in the revised Ghent criteria; however, there are multiple gene mutations, so there can be false-negative results. For a clinical diagnosis of Marfan syndrome, in the absence of family history, an affected person should display major criteria in at least two organ systems and involvement of a third organ system. In the presence of a positive family history, an affected person should display one major criterion in an organ system and involvement of a second organ system [7].

Exam features associated with MFS include a high-arch palate, small narrow jaw, and arachnodactyly—which can be determined by having the patient make a fist and looking for the thumb to protrude or having the patient wrap his or her pinky and thumb around his or her wrist (Fig. 50.2).

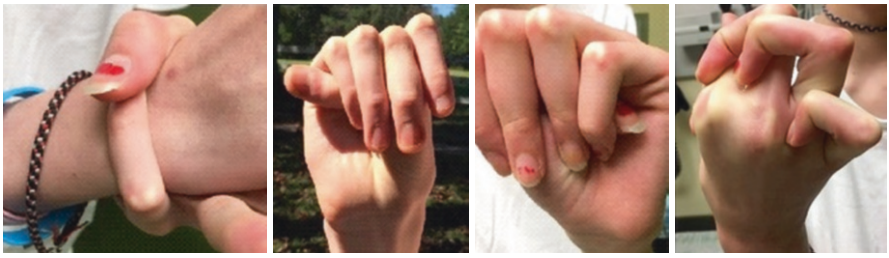


Fig. 50.2 Exam findings of Marfan syndrome due to arachnodactyly

Orthopedic Features of Marfan Syndrome

Table 50.1 reviews orthopedic features of Marfan syndrome.

Spine

Scoliosis is present in 60% of patients with Marfan syndrome; it is the most common skeletal abnormality in patients with MFS (Fig. 50.3). The diagnosis of scoliosis should be confirmed with full-length scoliosis films. The scoliosis in MFS often has rapid progression with poor response to bracing (17% success rate when compared to adolescent idiopathic scoliosis rates of 74–94%) [7]. Moreover, the vertebral shape is affected, which makes operative treatment challenging. This includes narrow pedicles, vertebral and sacral scalloping, wide transverse processes, thin laminae, and low bone mineral density [9]. Surgical intervention for scoliosis is indicated for a rapidly progressive curve or a curve of a large magnitude. Curves tend to progress when they hit a magnitude of 30° and become more severe when they hit a magnitude of 50° [7]. Growing rods may be indicated in a younger MFS patient. The complication rate is much higher in patients with MFS when compared to adolescent idiopathic scoliosis. Complications include hardware failure (due to thin laminae, thin pedicles, and osteopenia), infection, pseudarthrosis, dural tear and intraoperative CSF leak, and need for reoperation due to decompensation of the curve [10].

Spondylolisthesis is more common in patients with Marfan syndrome; it occurs twice as often when compared to the general population. The slip angle also tends to be double that of the general population. If spondylolisthesis is symptomatic, surgical intervention is recommended [8]. Prior to surgery, a MRI should be obtained to rule out dural ectasia (Fig. 50.4).

Other spinal defects can cause issue; for instance, if the thoracic lordosis is coupled with a pectus excavatum deformity—some sort of chest deformity, excavatum or carinatum, present in 66% [7]—the AP diameter of the chest is reduced causing compression of the large airways and increasing the risk of infections [9]. Surgical intervention for the pectus excavatum deformity would be necessary in this case rather than a cosmetic surgery.

Table 50.1 Orthopedic features of Marfan syndrome [8], https://www.omim.org/entry/154700

Spine	Pelvis	Limbs	Hands	Feet	Other
Scoliosis Kyphoscoliosis Thoracic lordosis Spondylolisthesis Lumbosacral dural ectasia	Protrusio acetabuli	Dolichostenomelia Joint hypermobility Joint contractures Genu recurvatum	Arachnodactyly	Pes planus Long, narrow feet Pes cavus Hammer toes Medial rotation of the medial malleolus	Early arthritis

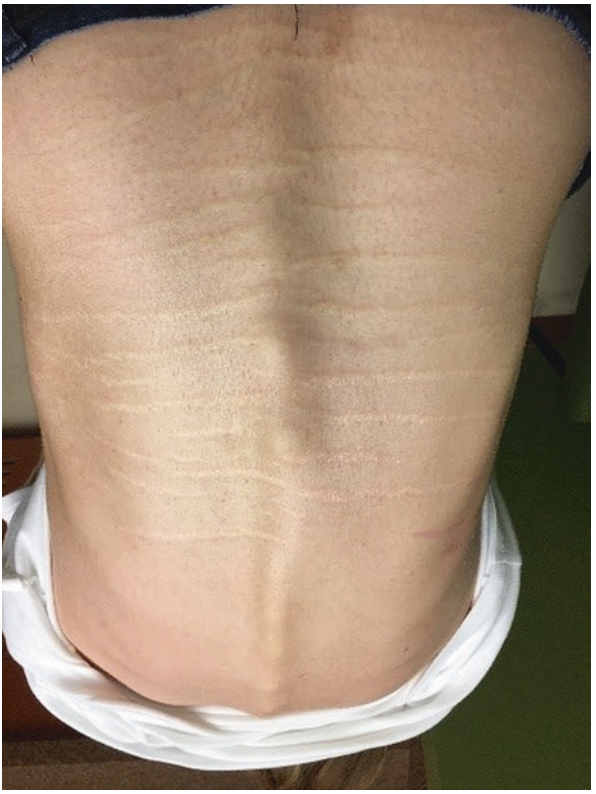


Fig. 50.3 A patient with curvature of the spine as well as striae—common findings in Marfan syndrome

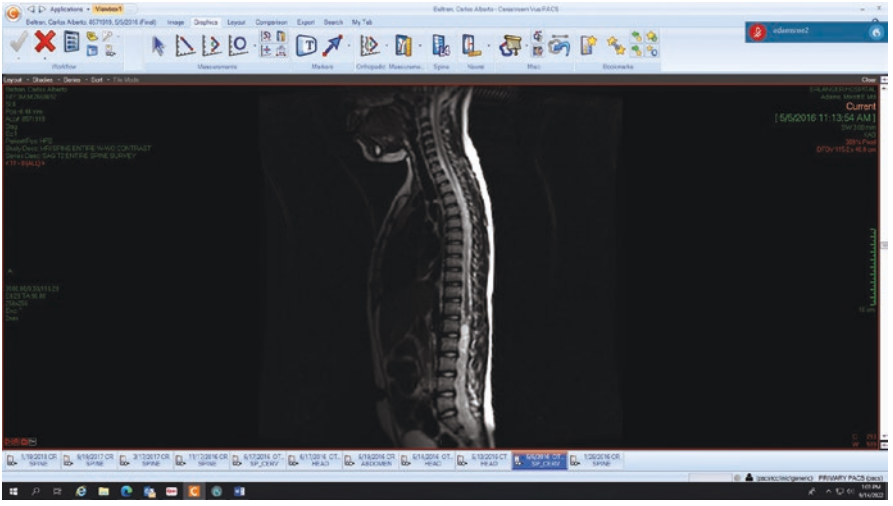


Fig. 50.4 MRI findings of dural ectasia. Dural ectasia may clinically present as headache and back pain

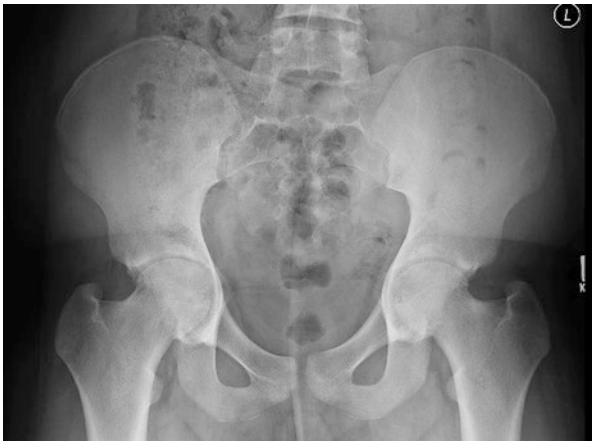


Fig. 50.5 X-ray of a patient with mild bilateral acetabular protrusion. Presenting as hip pain to an outpatient pediatric orthopedic clinic

Pelvis

Protrusio acetabuli may present as hip pain in the patient with MFS. Diagnosis may be made by obtaining an X-ray of the pelvis (Fig. 50.5). Treatment is conservative unless causing pain. Management of this can include closure of the triradiate cartilage in a skeletally immature patient to help disrupt and decrease the progression, although this is controversial and there is not enough evidence to recommend. In older patients, valgus intertrochanteric osteotomy and eventually definitive treatment with total hip arthroplasty are the only methods available for correction of the protrusio acetabuli [11].

Extremities

Joint hypermobility is a common shared finding in all connective tissue disorders. It is often a difficult problem to treat. Musculoskeletal manifestations may include recurrent joint sprains and ligament and tendon injuries. Recurrent joint subluxations or dislocations may also be more serious complications. The mainstay of treatment is physical therapy and adaptive bracing, and in case of recurrent dislocations, surgical intervention may be warranted.

Feet

Pes planus of the feet in Marfan syndrome, present in 25% of patients [7] (Fig. 50.6), tends to be due to the extreme hypermobility and is associated with ankle valgus

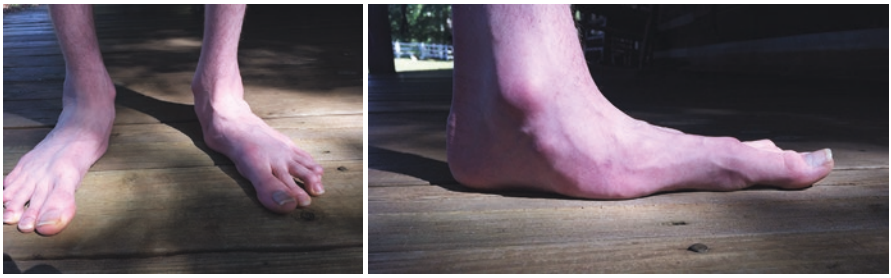


Fig. 50.6 Pes planus seen in Marfan syndrome due to extreme hypermobility

deformities. It may be a source of pain and fatigue for patients. Orthotics are the mainstay of treatment, although if severely painful surgical intervention can be done despite being rarely indicated or fully successful.

References

1. Yang H, Ma Y, Luo M, Zhao K, Zhang Y, Zhu G, et al. Identification of gross deletions in FBN1 gene by MLPA. Hum Genomics. 2018;12(1):46.
2. Dietz H. Marfan syndrome. In GeneReviews at GeneTest: medical genetics information resource (database online). University of Washington, Seattle; 1997–2011. http://www.genetests.org.
3. Loeys BL, Dietz HC, Braverman AC, Callewaert BL, De Backer J, Devereux RB, et al. The revised Ghent nosology for the Marfan syndrome. J Med Genet. 2010;47(7):476–85.
4. Reinhardt D, Keene D, Corson G, et al. Fibrillin-1: organization in microfibrils and structural properties. J Mol Biol. 1996;258:104–16.
5. Zhang H, Hu W, Ramirez F. Developmental expression of fibrillin genes suggests heterogeneity of extracellular microfibrils. J Cell Biol. 1995;129:1165–76.
6. Adams J, Trent R. Aortic complications of Marfan's syndrome. Lancet. 1998;352:1722–3.
7. Giampietro P, Raggio C, Davis J. Marfan syndrome: orthopedic and genetic review. Curr Opin Pediatr. 2002;14(1):35–41.
8. Online database OMIM database. Johns Hopkins University, 1966–2018. Entry #154700. https://www.OMIM.org. Accessed 16 Oct 2018. Online Mendelian Inheritance in Man, OMIM®. Johns Hopkins University, Baltimore, MD. MIM Number: Entry #154700: {Date last edited}: World Wide Web URL: https://omim.org/. Accessed 16 Oct 2018. Contributors: Jane Kelly—updated: 07/14/2015; Creation Date: John F. Jackson: 6/15/1995; Edit History: joanna: 07/14/2015.
9. Child A. Non-cardiac manifestations of Marfan syndrome. Ann Cardiothrac Surg. 2017;6(6):599–609.
10. Zenner J, Hitzl W, Meier O, Auffarth A, Koller H. Surgical outcomes of scoliosis surgery in Marfan syndrome. J Spinal Disord Tech. 2014;27(1):48–58.
11. Van de Velde S, Fillman R, Yandow S. Protrusio acetabuli in Marfan syndrome. History, diagnosis and treatment. J Bone Joint Surg Am. 2006;88(3):639–46.

Chapter 51
Turner Syndrome

Ehab H. Yasin

Introduction

Turner syndrome (also known as monosomy X, 45X, and Ullrich-Turner syndrome) is a non-inherited, neurogenetic disorder characterized by the complete or partial absence of an X chromosome that only involves females. While many various genetic variations can exist within Turner syndrome [1], complete or partial loss of a sex chromosome can result in multiple consequences in regard to the body's overall health and development. While genetic testing continues to be helpful in identifying aspects of the disease, specifically growth-related genes, not all genes have been identified [2].

Many of the orthopedic consequences in regard to the body's overall health involve both the quality of bone (bone mineral density) and the speed of bone growth. Given that most patients with Turner syndrome end up being on hormone therapy due to decreased estrogen/growth hormone levels in the blood, the titration of these hormones as a patient continues to grow and develop is difficult to regulate. Patients are being considered to start exogenous growth hormone therapy as early as 4 years old in some cases [1]. With the push for earlier intervention, routine follow-up appointments are also being recommended, roughly every 4 months during the initiation phase (first year) of growth hormone, and should continue to follow up at a minimum of every 6 months while continuing therapy. If multiple exogenous agents are used, that follow-up period may increase in frequency for further medication titration [1]. Patients with Turner syndrome benefit from routine follow-ups at comprehensive Turner syndrome clinics with the following groups: endocrinology, reproductive endocrinology, cardiology, otolaryngology, audiology, genetics, kidney

E. H. Yasin (✉)
Department of Physical Medicine and Rehabilitation, Rush University Medical Center, Chicago, IL, USA
e-mail: ehab_h_yasin@rush.edu

J. F. Sarwark, R. L. Carl (eds.), *Orthopaedics for the Newborn and Young Child*,
https://doi.org/10.1007/978-3-031-11136-5_51

diseases, neuropsychiatry, nutrition, and ophthalmology. While some members of this treatment team may be seen more often than others depending on individual patient needs, hormonal imbalance can consequently cause asymmetric growth speeds in certain skeletal growth areas. While on agents that modulate growth or bone health in general, evaluation for leg length discrepancies and scoliotic changes should be performed during these follow-ups so that proper referrals are made for early intervention to correct and/or accommodate these changes.

Skeletal conditions typically seen in Turner syndrome include short stature (very common), growth failure (very common), increased upper to lower limb segment ratios (very common), cubitus valgus (common), scoliosis ($1/5$ of population), exaggerated kyphosis (common), short cervical neck ($1/3$ of population), genu valgum ($1/3$ of population), pes planus, short metacarpals ($1/3$ of population), and Madelung deformities (5% of population) to name a few [3].

Epidemiology

Turner syndrome affects approximately 1 in 2000–2500 female live births [4]; however, roughly 1% of fetuses with 45X (most common variation) can survive to term [4]. The disorder has been diagnosed prenatally and postnatally due to advancements in prenatal testing and techniques (ultrasonography vs. amniocentesis vs. chorionic villus sampling). Prenatal suspicion for the disease can be guided by ultrasound evidence of cystic hygromas, congenital heart defects, and other structural defects [5].

While it is known that the prevalence of Turner syndrome is higher at conception versus at birth, the prenatal diagnosis is not always correct given the many chromosomal mosaic variations in this disease. Ethics challenges make it difficult to assess stillbirth/miscarriages to determine if the prenatal diagnosis is correct. More research is required to properly diagnose prenatal cases of Turner syndrome [6].

Pathophysiology

As discussed earlier, Turner syndrome is caused by complete loss (monosomy) or partial absence of the second sex chromosome during conception and embryo development. There are a variety of known genetic karyotypes, where only a certain portion of the chromosome may be affected. This is referred to as mosaicism. Mosaicism allows for individuals to have the varying physical presentations of the disease.

Most symptoms of Turner syndrome are suspected to occur because of the loss of genetic material on the missing X chromosome. So far, one gene has been shown to play a role in the bone and growth development of Turner syndrome. The short

stature homeobox gene, aka SHOX gene, is identified as being involved in the growth and maturation of the skeleton. The absence of this gene in Turner syndrome explains the very common finding of short stature and other skeletal abnormalities [1].

Common Clinical Presentation

As discussed earlier, clinical presentations observed in utero that show common sonographic findings such as cystic hygromas, congenital heart defects, and increased nuchal translucency can guide the suspicion for genetic testing or if amniocentesis has been performed.

The common phenotypic features observed in females with this syndrome would further guide physicians to seek genetic testing for this syndrome.

Most females with Turner syndrome are often diagnosed at birth, given improved diagnostic testing and more awareness about the syndrome. This can be due in part to the physical features shown, including but not limited to short necks, webbed necks, and lymphedema in the dorsum of the hands and feet [7] and wide-set nipples, among other facial characteristics. These can also go along with cardiac and renal abnormalities noted prenatally. As the child ages, signs of short stature are the most common when compared to peers in their age group; increased cubitus valgus as well as certain facial characteristics, including droopy eyes, low-set ears, neck webbing, low posterior hairline approaching their shoulders, receding jaws, high-arched palates, and crowded teeth, can all help phenotypically trigger further genetic testing to obtain a diagnosis. Patients can also have a neurocognitive delay, where typically verbal domains present as strengths while impairments are noted in visual-spatial, executive function, and emotion processing [2]. Patients can also have impairments in hearing and recurrent middle-ear infections.

As the child continues to age into preteen years with underdeveloped sex features and delayed onset of puberty, along with the above-noted physical features, the clinical phenotypic picture begins to come together to trigger further testing and treatment.

Some patients, however, progress through their life into adulthood with minimal physical features/complications of the syndrome. Diagnosis can be delayed into adulthood in these cases. If the physical findings are minimal, oftentimes investigations into infertility as adults can lead to this diagnosis, as patients with Turner syndrome have difficulty naturally conceiving a child [8].

Diagnosis is made by phenotypic features found on the physical exam and testing, including genetic testing and chromosome analysis. From a skeletal perspective, generally, these patients are asymptomatic with minor to no functional deficits. Further imaging of specific joints would be dependent on physical exam findings. Many of the skeletal concerns are more a result of the poor hormone balance. With the increased recommendations for hormone repletion at young ages in this population, symmetric bone growth and optimal bone health are of highest priority from an orthopedic perspective.

Orthopedic Conditions Commonly Seen in Turner Syndrome

While gonadal dysgenesis can cause many skeletal abnormalities, we will focus on the more common findings in Turner syndrome listed below.

Short Stature: Most common feature of Turner syndrome, found in roughly 90% of all diagnosed, with an average height of 54–60 inches [7]. Treatment of short stature is dependent on the initiation of growth hormone. If treatment is initiated prior to growth plate closure, it will often have an increase in growth.

Delay in Skeletal Maturation: It was previously more difficult in younger children to note a delay in skeletal maturation; however, the older the child became, the more prevalent the delay became. This delay is due to the failure of the growth plates to close [7].

Osteoporosis: Significant hormone utilization deficiencies noted in Turner syndrome secondary to the ovarian dysgenesis leave patients at risk for developing osteoporosis. While common in Turner syndrome, patients are at increased risk for developing an increased thoracic kyphosis and scoliosis of the spine [1]. It has yet to be proven that exogenous hormone replacement in this specific population has decreased the incidence of osteoporosis. However, improved early diagnostic techniques and earlier initiation of hormone therapy to bring about the onset of puberty are something to further monitor, as patients get older and transition into adulthood [7].

Excessive Kyphosis: The prevalence of excessive kyphosis with vertebral body wedging was shown to be increased in early teenage populations of females with Turner syndrome on radiographs. Radiographic evaluation on routine visits as part of a Turner syndrome treatment team should be considered as early detection and intervention can be initiated to slow the process and prevent further structural abnormalities [9].

Scoliosis: Approximately 10% of girls with Turner syndrome develop scoliosis, most commonly during their adolescent years. The etiology of the scoliosis is likely multifaceted given the natural progression of Turner syndrome and with the exogenous hormone supplementation [1]. Patients with Turner syndrome have an increased risk for scoliosis, coupled with growth hormone initiation at young ages; they will need to be monitored more frequently for scoliotic changes. Prevalence is noted to increase with age and height in patients on growth hormone therapy versus those not on growth hormone therapy (69–35%) [10]. As one would suspect with rapid periods of growth in adolescence, ligament and muscle length does not necessarily increase at the same speed. Given the treatment guidelines focused on the initiation of growth hormone earlier in females with Turner syndrome, consideration should be made for a prolonged period of observation (until age 20) for identifying scoliosis. No data is currently available that shows the timing of hormone replacement and progression of scoliosis. However, with this more frequent monitoring period in adolescent to teenage years, research and implementation of a treatment/rehabilitation program when scoliotic changes are radiographically evident would help delay/prevent complications common to all types of scoliosis [10].

Growth Plate Abnormalities: Often the site of subtle irregularities that produce subtle irregular arching and overlying adaptive changes in the child's bones. These subtle distortions can be associated with premature closure or subtle functional changes in the child's joint. Dr. RK Beals gave an example of this in his published literature from 1973, which discussed "*a medial projection of the proximal metaphysis beyond the epiphysis, depression of the medial plateau, superior and inferior beaking of the medial border of the overlying epiphysis, and slight elevation of the fibular head. The overlying medial femoral condyle is often enlarged, resulting in a lateral shift of the tibia, that was present in 7/11 patients with radiographs*" [7].

Genu Valgum: Given the above description, "knock-knee" has a prevalence of 63–86% in Turner syndrome [1]. Even though a wide range is noted, it is a common feature. While this typically is present between normal children 18 months to 6 years of age, the presence is symmetric, with peak valgum at age 4, and begins to realign with slight valgum between ages 6 and 7. If the valgum worsens after age 4, becomes asymmetric, or remains excessive after age 7, further evaluation is needed, starting with a more thorough physical exam and radiographs [11]. Addressing this in childhood sooner will help delay the onset of knee arthritis or patellofemoral syndrome in these patients as adults.

Pes Planus: "Flatfeet" have a prevalence of 31% in Turner syndrome and can further exacerbate hip and knee problems [12]. This is further exacerbated by a valgus deformity of the subtalar joint. Foot arch malformation is in equal proportion of splayfoot vs. low arched found in $^{2}/_{3}$ of women with Turner syndrome, where the transverse arch is more affected than the longitudinal arch. Proper musculoskeletal assessment to determine the flexibility of arches will further guide corrective treatment, be it orthotic or surgical management [12].

Developmental Dysplasia of the Hip: Often screened and seen at birth as patients with Turner syndrome have an increased risk as compared to the general population. Females are also more frequently affected than males on a ratio of 4:1 in non-Turner syndrome populations [11]. Continued screening and evaluation should continue through the first 9 months of infancy. The effect of hip dysplasia depends on its level of severity. However, asymmetry in the hips in any capacity, be it alignment or full dislocation, can contribute to the development of osteoarthritis in the hips, as females get older [13]. The goals of treatment if identified in a patient with Turner syndrome should be similar to that of a non-Turner syndrome patient. As early as possible, obtain and maintain a concentric reduction of the hip without force and by avoiding extremes of position dependent on the patient's age [11].

Cubitus Valgus: Increased carrying angle of the elbow has a reported prevalence of 70–80% of patients with Turner syndrome [1]. While treatment is typically non-surgical unless ulnar nerve neuritis presents or decreased functional use of the elbow occurs, this is more of an identifying feature in patients with Turner syndrome, but should remain on the differential given the bone abnormalities discussed below with the wrist, radius, and ulna [7].

Distal Radioulnar Disparity and Madelung Deformity: Distal radioulnar deformities are very common in those diagnosed with Turner syndrome, appearing in roughly 80–90% of the population [1]. As stated earlier, minor growth plate

disturbance can affect the length or thickness of a bone and, in turn, the neighboring joint. In the case of distal radioulnar deformities, a flattened epiphysis with resultant alteration of form in the hand is very common. The distal radial growth plate begins to arch, growth on the volar/ulnar portion of the distal radial physis is retarded, and the carpals migrate proximally, producing a Madelung deformity [7]. While the radioulnar disparity is more common, a Madelung deformity only appears in roughly 10% of those with Turner syndrome [1]. This deformity is typically noted to be bilateral, but asymmetric in severity. Mild Madelung deformity is not treated, but more severe deformities may require surgical intervention, to preserve functional mobility in the wrist and decrease pain. If the deformity continues to progress, a decreased radioulnar angle, lunate subluxation, and various degrees of dorsal subluxation of the distal ulna would occur. The typical patient with a Madelung deformity presents with severe pain, or cosmetic discomfort often requiring surgical correction [14]. While multiple Madelung deformity corrections have been performed (performing surgery on the radius, ulna, or both bones including surrounding soft tissues), there is no clear consensus on the best approach for correction.

Treatment and Management

As discussed earlier, a comprehensive approach with other treatment teams is essential when approaching a patient with Turner syndrome. Phenotypic findings suspicious for the disease often lead to further genetic karyotyping. While hormone supplementation is essential in the treatment of symptoms related to the disease, preserving existing function, maintaining adequate range of motion, and prevention of future joint problems should be the goal of any orthopedist evaluating these patients. The most common reasons a patient would be referred to an orthopedic surgeon were discussed above, including common findings of poor or asymmetric growth and limb deformity with the elbows, wrists, hips, or knees. In addition to the physical exam, appropriate radiographs should be obtained for the area of concern. The high incidence of skeletal abnormalities observed in this population necessitates continued skeletal monitoring throughout childhood into late teenage years. Those identified with more severe bone abnormalities in childhood will likely continue to need orthopedic care well into adulthood.

References

1. Gravholt C, Andersen N, Conway G, Dekkers O, Geffner M, Klein K, et al. Clinical practice guidelines for the care of girls and women with Turner syndrome: proceedings from the 2016 Cincinnati International Turner Syndrome Meeting. Eur J Endocrinol. 2017;177(3):G1–G70.
2. Kesler S. Turner syndrome. Child Adolesc Psychiatric Clin North Am. 2007;16(3):709–22.
3. Approximate incidence of major clinical abnormalities in Turner syndrome. Uptodate.com. 2019. https://www.uptodate.com/contents/image?topicKey=7391&search=&source=outline_link&imageKey=ENDO%2F60006.

4. Papp C, Beke A, Mezei G, Szigeti Z, Bán Z, Papp Z. Prenatal diagnosis of Turner syndrome. J Ultrasound Med. 2006;25(6):711–7.
5. Loscalzo M, Bondy C, Biesecker B. Issues in prenatal counseling and diagnosis in Turner syndrome. Int Congr Ser. 2006;1298:26–9.
6. Gravholt C, Juul S, Naeraa R, Hansen J. Prenatal and postnatal prevalence of Turner's syndrome: a registry study. BMJ. 1996;312(7022):16–21.
7. Beals R. Orthopedic aspects of the XO (Turner's) syndrome. Clin Orthopaed Related Res. 1973;97:19–30.
8. Abir R. Turner's syndrome and fertility: current status and possible putative prospects. Hum Reprod Update. 2001;7(6):603–10.
9. Elder D, Roper M, Henderson R, Davenport M. Kyphosis in a Turner syndrome population. Pediatrics. 2002;109(6):e93.
10. Ricotti S, Petrucci L, Carenzio G, Klersy C, Calcaterra V, Larizza D, et al. Prevalence and incidence of scoliosis in Turner syndrome: a study in 49 girls followed-up for 4 years. Eur J Phys Rehabil Med. 2011;47(3):447–53. https://www.minervamedica.it/en/journals/europa-medicophysica/article.php?cod=R33Y2011N03A0447.
11. Cramer K, Scherl S, Hurley R, Caputo G, Rampertab R, Quigley K. Pediatrics. 1st ed. Philadelphia: Lippincott Williams & Wilkins; 2004.
12. Trzcińska D, Olszewska E, Wiśniewski A, Milde K, Madej M. The knee alignment and the foot arch in patients with Turner syndrome. Pediatr Endocrinol Diabetes Metab. 2011;17(3):138–44. https://www.ncbi.nlm.nih.gov/pubmed/22027067.
13. Frias J, Davenport M. Committee on genetics, section on endocrinology. Health supervision for children with Turner syndrome. Pediatrics. 2003;111(3):692–702.
14. Staheli L. Fundamentals of pediatric orthopedics. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2003.

Suggested Reading

Current References including applicable position statements and most recent recommendations from the American Academy of Pediatrics.
https://pediatrics.aappublications.org/content/140/5/e20172626.

Chapter 52
Cerebral Palsy

Vineeta T. Swaroop

Background

Cerebral palsy (CP) is a term used to describe a group of conditions of differing severity with certain developmental features in common. The consensus definition formed by an international panel in the 2000s is: "Cerebral palsy describes a group of permanent disorders of the development of movement and posture, causing activity limitation, that are attributed to nonprogressive disturbances that occurred in the developing fetal or infant brain. The motor disorders of cerebral palsy are often accompanied by disturbances of sensation, perception, cognition, communication and behavior, by epilepsy and by secondary musculoskeletal problems" [1]. CP is the most common cause of physical disability affecting children in developed countries.

While the lesion to the immature brain which causes CP is nonprogressive, it is important to understand that the resulting disorders of posture and movement are permanent but not unchanging [2]. The musculoskeletal pathology accompanying CP is progressive, a fact which should be understood by both providers and patients and their families. From the orthopedic standpoint, most newborn children with CP have no deformities or musculoskeletal abnormalities. Rather, the characteristic orthopedic manifestations, such as scoliosis, hip dislocation, and fixed contractures, develop over time with growth and will most likely continue to have an effect over the whole life span. Because of this, CP needs to be thought of and managed in the context of development, functioning, and family [3].

V. T. Swaroop (✉)
Department of Orthopaedic Surgery, Ann & Robert H Lurie Children's Hospital of Chicago, Chicago, IL, USA
e-mail: vtswaroop@luriechildrens.org

J. F. Sarwark, R. L. Carl (eds.), *Orthopaedics for the Newborn and Young Child*,
https://doi.org/10.1007/978-3-031-11136-5_52

Epidemiology/Pathophysiology

CP, affecting 1 in 500 neonates, is the most common childhood-onset neuromuscular disorder with an estimated prevalence of 17 million people worldwide [3]. A number of factors have contributed to a modest increase in the prevalence of CP in developed countries including the increased survival of very premature infants and a rise in multiple births [2, 4].

Traditionally, patients with CP were recognized to have two factors in common: premature birth and neonatal oxygen deprivation. Both were considered as known causes or risk factors for CP along with low birth weight (less than 1500 g), placental abnormalities, fetal growth retardation, perinatal stroke, and multiple births [5–7]. Now, however, particularly with regard to prematurity and oxygen deprivation, these issues are considered more indicative of factors operating earlier in development, rather than direct causes of CP. Careful epidemiological and brain imaging studies suggest that CP often has intrauterine antecedents and is commonly multifactorial. Recent studies point to factors such as fetal inflammation, chorioamnionitis, low maternal thyroid hormone levels, and hypocapnia in association with mechanical ventilation [8–11]. Regardless of the specific etiology, the common link is an insult to the developing motor system in the brain. This could include the motor cortex, periventricular regions, or basal ganglia (dystonia).

With an improving understanding of the complex interrelation of perinatal abnormalities and biological processes that lead to the development of CP, much research is being devoted to investigating potential interventions to address both primary prevention and secondary mitigation of the effects of the brain injury. For instance, several recent trials have shown that CP is decreased by 30% in premature infants whose mothers received magnesium sulfate during labor [12, 13]. Similarly, antenatal steroids administered prior to 34 weeks of gestation have also shown to be effective in reducing the risk of CP [14]. Another important advance is the discovery of a decline in the prevalence of CP with 72 h of brain or body cooling in full-term infants with birth asphyxia [15].

Common Clinical Presentation: History and Physical

There are many important components in the medical history of a patient with CP being seen for the first time by the orthopedist. A detailed birth history should be obtained including birth weight, gestational age, and any pregnancy or delivery complications. Developmental history includes the age at which head/neck control was obtained, as well as independent sitting, standing, and achievement of ambulation if applicable. The provider should ask about any preferential use of limbs or abnormal tone. As appropriate, an assessment of current functional ambulatory

capacity in the home, school, and community should be included as well as other skills such as stairs, jumping, and running. Any orthoses, assistive devices, or wheeled mobility utilized should be noted. Providers should ask about physical therapy regimen, accommodations in school, and medications. Concomitant medical history should be obtained including history of seizure, respiratory problems, feeding issues, or behavior or learning difficulties.

All of this information helps the provider to understand the individual situation of a patient with CP. The birth history and concomitant medical diagnoses help with goal setting and determining diagnosis and prognosis. Attainment of developmental milestones provides insight into a patient's future functional capacity [16]. If considering surgical treatment, any previous operative reports should be reviewed to understand the history behind current deformities and compensations [16]. Most importantly, the provider should ask about the reason for referral and specific questions and goals of the patient and family.

The comprehensive physical examination of a child with CP includes seven broad categories: strength and selective motor control of isolated muscle groups; abnormal muscle tone; upper and lower extremity range of motion; scoliosis, torsion, and other bony deformities; fixed and mobile foot deformities; balance, equilibrium responses, and standing posture; and gait [16].

Radiographic Studies/Testing/Evaluation

Arriving at a formal diagnosis of CP can be challenging due to the varying clinical manifestations, which occur over different time courses. Initially, the presence of developmental delay and failure to meet milestones combined with persistence of primitive reflexes and/or muscle tone abnormalities may lead to a clinical suspicion for CP. The differential diagnosis includes other metabolic, neurodegenerative, or genetic disorders, which should be suspected if a patient loses previously acquired motor milestones. Brain MRI is often part of the workup of a patient suspected to have CP, and in fact the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society have recommended that, where possible, the clinical diagnosis of CP should be confirmed by imaging [17]. Brain MRI has been found to be abnormal in 86% of patients with CP [18]. However, there is considerable heterogeneity in the clinical significance of imaging findings. As such, the diagnosis of CP is typically made based on the combination of clinical and imaging methods.

A very important evaluation tool in the orthopedic management of patients with CP is computerized gait analysis (CGA). CGA, which has been used in children with CP since the 1970s, helps to support clinical decision-making for preoperative planning for orthopedic surgery and selective dorsal rhizotomy and is useful in

assessing the outcomes of interventions. The components of gait analysis may include kinematics, kinetics, electromyographic data, measurement of videotape recordings, energy expenditures, clinical observation, and foot pressure readings [19]. The data obtained are presented as graphic and numerical data (Fig. 52.1), electromyographic activity, and videotape recordings, all of which are then reviewed by a specially trained clinician in order to generate a report on the interpretation of the gait analysis. Gait analysis data has led to a much deeper understanding of the processes driving pathologic gait patterns and hence identification of appropriate interventions to improve gait.

Neuromuscular hip subluxation is a common problem in CP, affecting up to 75% of patients with spastic quadriplegia. The effectiveness of a proactive surveillance program for early detection and management of hip subluxation has been well established [20–22]. Surveillance includes both clinical examination and radiographic examination with an anteroposterior pelvis radiograph at proscribed intervals

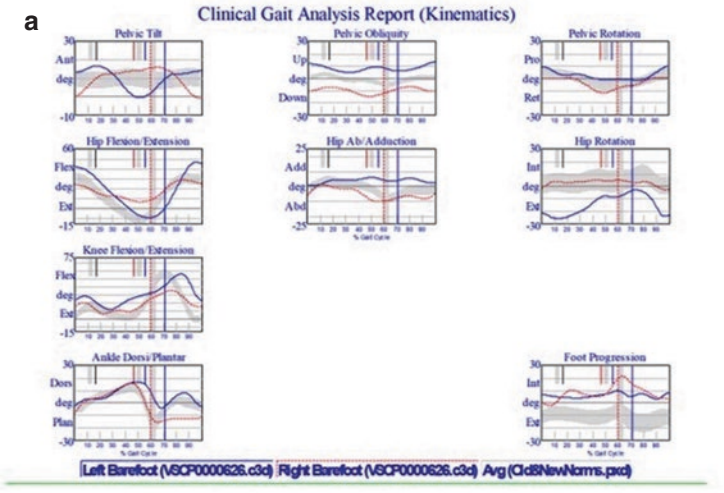


Fig. 52.1 Kinematic graphs obtained from computerized gait analysis (CGA) evaluation of an 11-year-old female with spastic diplegia, GMFCS level II. Each graph depicts one gait cycle, from initial contact (left side of graph) to the next initial contact (right side of graph). The vertical lines at approximately 65% of the gait cycle mark toe-off and separate stance phase (left of line) from swing phase (right of line). The range of normal motion is depicted by the gray shaded portion of the graph, while the left and right lower extremities are noted in blue and red lines, respectively. In this patient, the kinematic data (**a**) shows internal foot progression, especially on the right side. When examining the rotational breakdown data (**b**), one notes near-normal hip and tibial rotation; however, there is a dramatic internal rotation of the right foot. This case illustrates the value of CGA in identifying the precise location of pathology requiring surgical correction to improve gait. Adapted with permission from Motion Analysis Center, Shirley Ryan Ability Lab, Chicago, IL

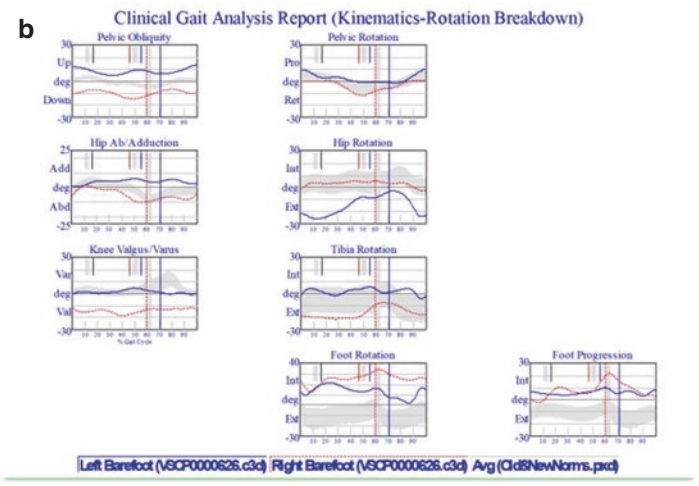


Fig. 52.1 (continued)

beginning at the age of 2 years for all patients with CP. Both components of screening, clinical examination and radiographs, are equally important since hip displacement can be clinically silent in the early stages when parents and clinicians may be focused on more obvious issues such as feeding difficulties and seizure management [2]. The frequency of serial clinical and radiographic examinations varies based on the functional level of involvement of the patient (Gross Motor Function Classification System, described in detail below). In general, ambulatory patients require less frequent screening than nonambulatory patients, who are known to have a higher risk for subluxation. Factors which would increase the frequency of surveillance for any patient include decreased hip range of motion, change in tone, deterioration in function, spinal deformity/pelvic obliquity, leg length discrepancy, and hip pain.

Detailed Description of Condition

Many different types of classifications exist to describe patients with CP, a fact reflective of the heterogeneity of etiology, pathophysiology, and hence clinical presentation across patients. One useful classification is the topographical classification, which reflects the location of insult to the motor cortex and the pattern of limb involvement (Fig. 52.2). Hemiplegia, often associated with perinatal ischemic stroke, affects one side of the body with the upper limb more affected than the lower limb. In spastic diplegia, often accompanied by periventricular white matter loss,

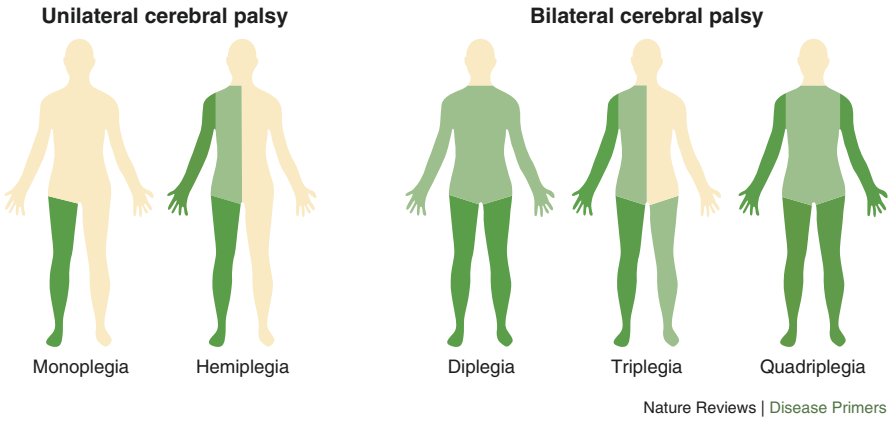


Fig. 52.2 Topographical classification of cerebral palsy depicts the pattern of limb involvement arising from the location of insult to the motor cortex. In hemiplegia, one side of the body is affected with the upper limb more so than the lower limb. In diplegia, both lower limbs are much more affected than the upper limbs. In triplegia, the pattern is unilateral upper limb involvement with bilateral, asymmetric lower limb involvement. The lower limb on the same side as the affected upper limb is more affected. In quadriplegia, all four limbs and the trunk are involved [3]. Reprinted by permission from Springer Nature: Nature Reviews Disease Primers. Cerebral Palsy, H. Kerr Graham, Peter Rosenbaum, Nigel Paneth, Bernard Dan, Jean-Pierre Lin et al. © Jan 7, 2016

both lower limbs are much more affected than the upper limbs. In triplegia, there is unilateral upper limb involvement combined with bilateral, and often asymmetric, lower limb involvement. Quadriplegia, associated with severe birth asphyxia, involves all four limbs and the trunk.

The topographic description of patients with CP also predicts function: the majority of children with hemiplegia ambulate independently; most with spastic diplegia ambulate but many require assistive devices; and those with quadriplegia are rarely able to functionally ambulate [2]. Overall, approximately 60% of patients with CP ambulate independently, 10% use a mobility device for ambulation, and 30% have limited or no functional ambulation [23].

While the topographic classification can accurately describe the pattern of limb involvement, it does not qualify the specific type of involvement. For this, the physiologic classification is useful to describe the nature of the movement disorder. The most common form, spasticity, is characterized by a velocity-dependent stretch reflex; in other words, an increase in muscle tone is seen with rapid passive stretching. Joint contractures frequently develop over time in patients with spasticity [23, 24]. In contrast, dystonia is characterized by sustained or intermittent muscle contractions causing abnormal, repetitive movements and/or postures [3]. Other less common movement disorders include chorea (jerky, dance-like movements), athetosis (slow, writing movements), ataxia (difficulty with coordinated movements and balance), and hypotonia (low muscle tone with abnormal reflexes).

By far, the most clinically useful development in the classification of CP has been the creation of the Gross Motor Function Classification System (GMFCS), used to describe motor function [25]. The GMFCS (Fig. 52.3) is a five-level grading

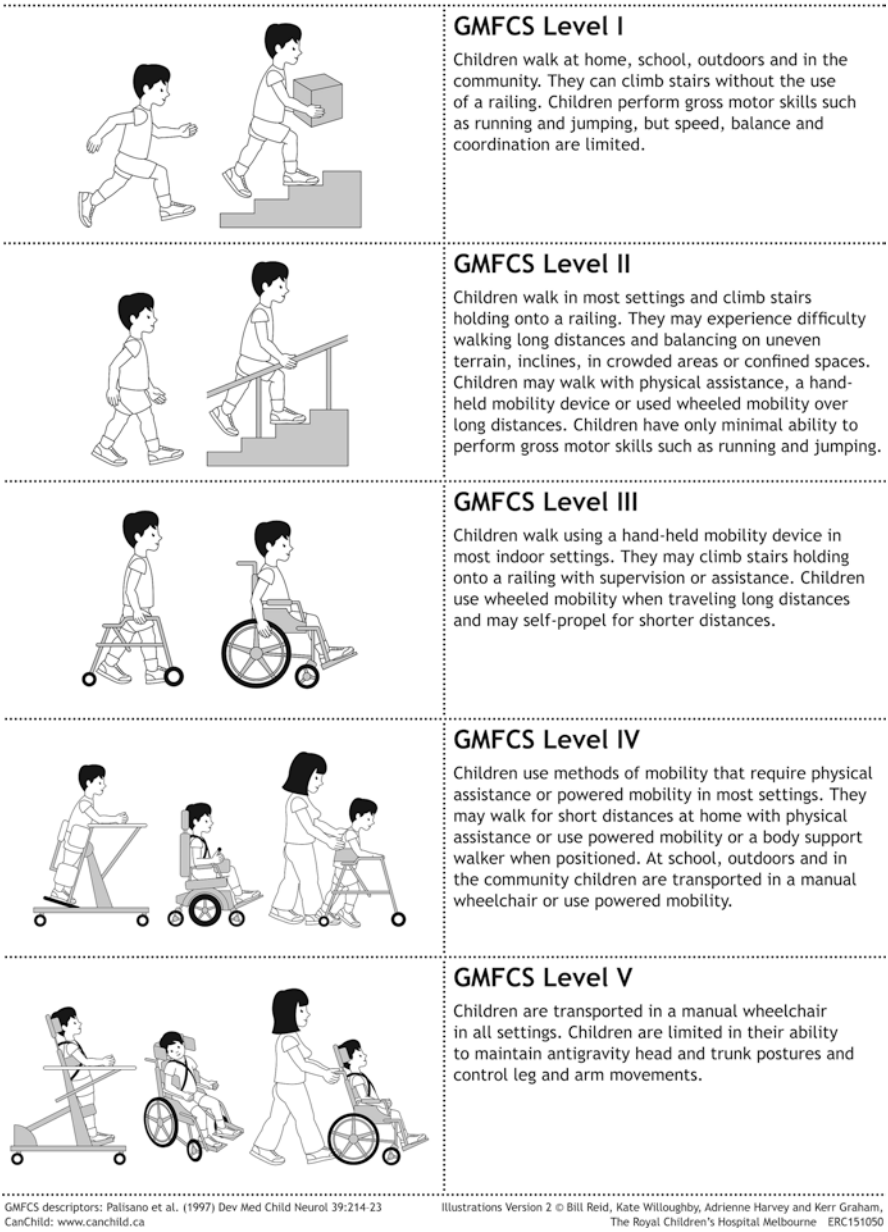


Fig. 52.3 Depiction of Gross Motor Function Classification System (GMFCS) expanded and revised for children with cerebral palsy, 6–12 years of age. The GMFCS has become the gold standard for classifying function in children with CP and has been shown to be valid, reliable, stable, and predictive of long-term gross motor function. The descriptors were devised by Palisano et al. [25]. Images are courtesy of B. Reid, A. Harvey and H.K.G., The Royal Children's Hospital, Melbourne, Victoria, Australia

system based on self-initiated movement emphasizing function with regard to sitting and walking. Differing age-based criteria have been developed, and the distinction between levels represents differences in gross motor function thought to be meaningful in the daily lives of children with CP [26]. An increased GMFCS level has been shown to correlate with increased risk of a number of orthopedic comorbidities including scoliosis and hip dislocation [27, 28].

In terms of musculoskeletal pathology in patients with CP, the central factor is failure of longitudinal growth of skeletal muscle [2]. Muscles in patients with CP have been found to be shorter and smaller and contain fibers of decreased diameter [3]. In addition, due to spasticity, skeletal muscle does not relax during activity. In general, children with CP have decreased activity levels due to weakness and poor balance. Contractures develop over time in part due to impaired longitudinal muscle growth and spasticity. Lever-arm dysfunction is a term used to describe the orthopedic deformities that develop in an ambulatory child with CP [29]. This describes the effect muscles and/or ground reaction forces exert on skeletal levers (long bones) to produce gait. Abnormalities of these lever-arm systems, due to bone modeling, remodeling, and/or traumatic deformities, can greatly interfere with a child's ability to walk [29]. An imbalance between growth of long bones and muscle-tendon units can lead to torsion of long bones (femoral anteversion, tibial torsion) and joint instability (hip subluxation, foot deformity). Premature degenerative changes in weight-bearing joints are common, and young adults with CP may experience pain which can be quite debilitating [30].

Treatment/Management

With the goal of maximizing function and participation, orthopedic management of patients with CP falls into three broad categories: management of weakness, spasticity, and fixed orthopedic deformities. Traditionally, clinicians have focused efforts toward addressing tone and deformities; however, more recognition is being given to the critical role weakness and balance deficits play in determining ambulatory prognosis.

More modern approaches to the treatment of patients with CP address muscle weakness as a common component of functional challenges with encouraging results [2]. To this end, physical therapy (PT) plays a critical role in treatment, especially from birth to age 3 and in postoperative periods. A recent study found long-term benefits from PT, most notably in younger, ambulatory patients (GMFCS Level II) [31]. Recent research has challenged the traditional view that muscle strengthening in patients with CP is undesirable for fear that it may increase spasticity. Rather, it has been shown that children with CP who participate in strengthening programs have increases in muscle power and improvements in function [32].

Treatment of spasticity is important in the attempt to delay the development of fixed contractures. Many methods exist to manage spasticity, including oral medications, botulinum toxin, and other injections, and for carefully selected patients, neurosurgical procedures such as intrathecal baclofen and selective dorsal rhizotomy are used. A recent systematic review found that botulinum toxin, oral diazepam, and selective dorsal rhizotomy were effective interventions for reducing muscle

spasticity [33]. It is important for providers to recognize and counsel families beginning at a young age that spasticity management is only one part of treatment for patients with CP. Many patients, despite having optimum spasticity management, will still go on to require orthopedic surgery to correct fixed deformities. However, proper spasticity treatment has been shown to delay fixed deformities and hence postpone the need for orthopedic surgery. This is of benefit since it is widely recognized that surgical outcomes are more predictable after 6 years of age. Families should be aware of the eventual potential need for orthopedic surgery from a young age and should understand that surgery is not a failure of management but rather another effective tool for the treatment of patients with CP.

Orthopedic surgical treatment is recommended once fixed musculoskeletal deformities arise in order to prevent decompensated joint pathology, such as a painful, degenerative dislocated hip. Once conditions such as this occur, surgical treatment options are limited, complication rates often increase, and outcomes are less satisfying. Two important longitudinal studies of gait in children with spastic diplegia confirm that the musculoskeletal pathology and resulting gait disorders are progressive during childhood [34, 35]. There is now definitive consensus that orthopedic surgery to address gait problems should correct all issues simultaneously, the so-called single-event multilevel surgery (SEMLS). SEMLS describes the correction of all fixed contractures and torsional deformities of the long bones during one operative session, requiring only one period of rehabilitation as a consequence. Ideally, SEMLS is performed between 6 and 12 years of age. Multiple studies have shown SEMLS results in large gait improvements, small improvements in gross motor function, and gains in all domains of the International Classification of Functioning [36–38].

The exact prescription for SEMLS depends on each individual patient's pathology in terms of tone, weakness, contracture, and deformity. Ideally, this is determined with the aid of a full biomechanical assessment in a computerized motion analysis laboratory. This formal gait analysis allows accurate dynamic assessment of the patient's particular gait problem. This in turn can help to distinguish underlying abnormalities requiring surgical treatment from the compensations which develop over time but do not require treatment other than correction of the underlying abnormality. Common components of SEMLS may include muscle tendon lengthening, tendon transfer, derotational osteotomy, and stabilization of the hip and foot. Some of the most frequent soft-tissue procedures include intramuscular lengthening of the psoas at the pelvic brim, intramuscular lengthening of the medial hamstrings, rectus femoris transfer, and gastrocnemius recession. Commonly performed bony surgeries include derotational osteotomies of the femur or tibia and osteotomies for correction of the valgus foot (Fig. 52.4).

Neuromuscular scoliosis is common in patients with CP and has been shown to increase in occurrence with increased GMFCS levels [28]. Especially in patients with higher GMFCS levels, spinal deformities are often rapidly progressive and occur in the setting of multiple medical comorbidities that may affect treatment and outcomes including epilepsy, respiratory disease, nutritional deficiencies, and osteopenia [2]. For these complex patients, surgery should be considered only in the context of multidisciplinary care, involving experts in the management of medical comorbidities, pain management, and pediatric intensive care.

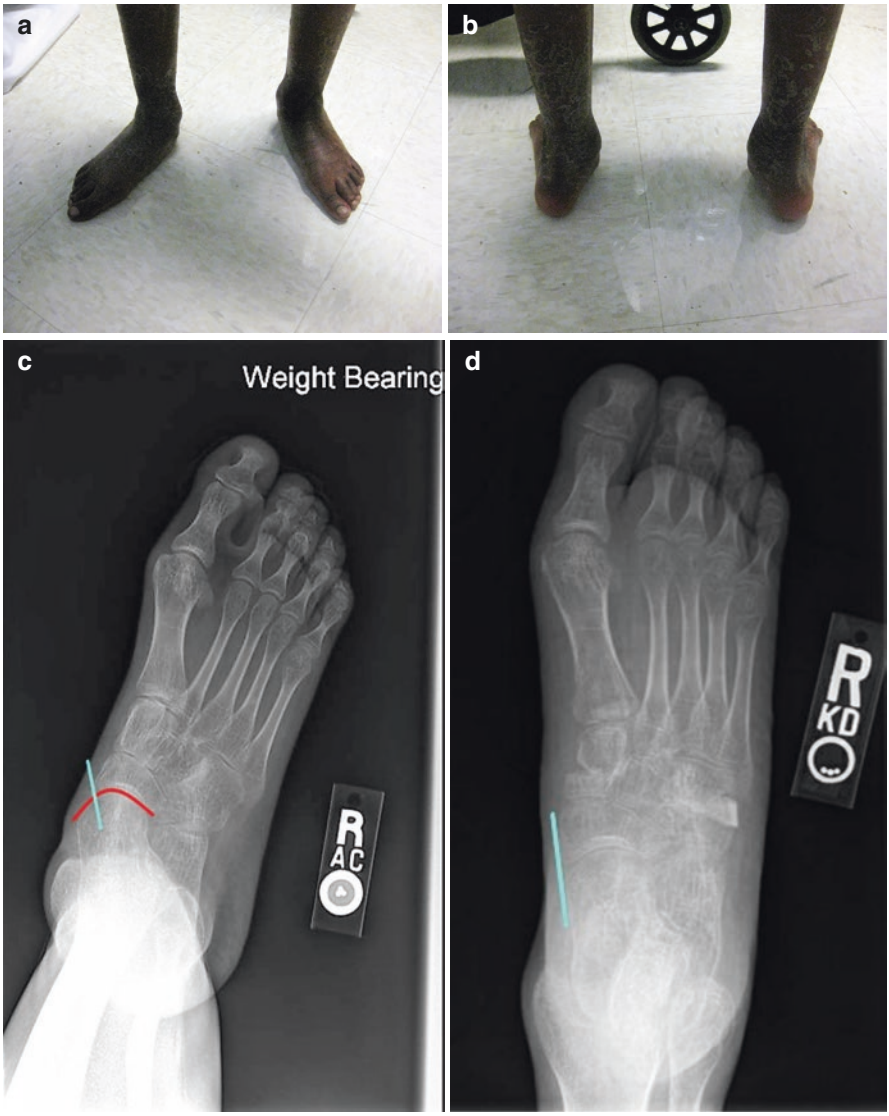


Fig. 52.4 11-year-old female with GMFCS level II spastic diplegia who has bilateral severe, rigid pes planovalgus. (**a**, **b**) Anterior and posterior clinical photographs demonstrating severe hindfoot valgus with collapse of the midfoot and forefoot abduction. She weight bears entirely on the medial border of her feet. (**c**) Preoperative anteroposterior radiograph of the right foot shows uncoverage of the talonavicular joint (talar head joint surface outlined in red, border of navicular marked by light blue line). (**d**) Postoperative anteroposterior radiograph after undergoing multiple foot osteotomies and soft-tissue lengthening demonstrates realignment of the talonavicular joint (light blue line). (**e**, **f**) Postoperative anterior and posterior clinical photographs demonstrating improved foot alignment with restoration of longitudinal arch and correction of hindfoot valgus and forefoot abduction

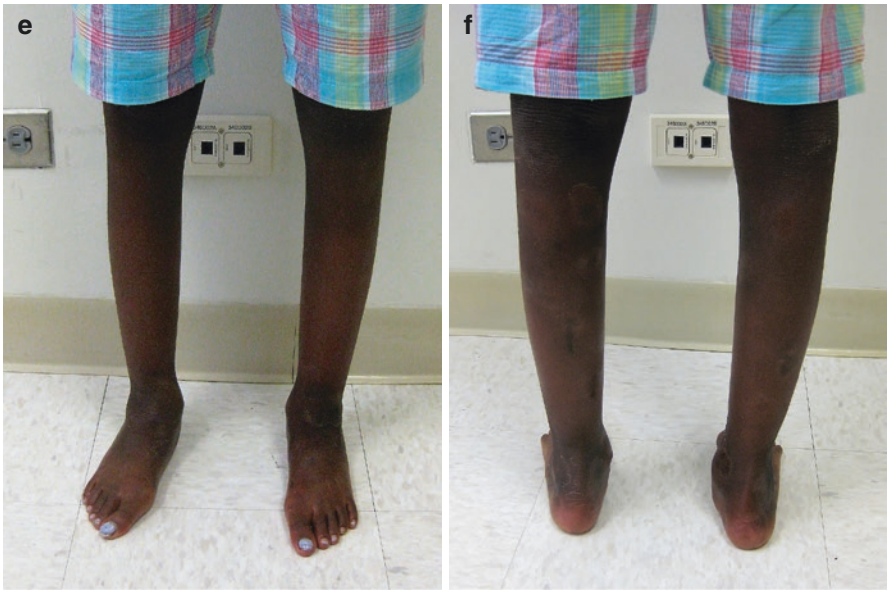


Fig. 52.4 (continued)

Nonsurgical methods for the management of neuromuscular scoliosis have disappointing outcomes. Bracing may be indicated to improve sitting balance but will not alter the course of curve progression [39]. Similarly, postural management and seating systems have not been well studied, and botulinum toxin injections have adverse effects and are not effective. When indicated, evidence supports surgical management of progressive scoliosis that compromises sitting balance with posterior spinal fusion and instrumentation [40] (Fig. 52.5). However, the decision to pursue surgical management must be made on an individual basis taking into account the specific risk-to-benefit ratio for each patient. While it is generally accepted that spinal deformities can be corrected surgically with acceptable complication rates in patients with CP, the evidence concerning quality-of-life outcomes is conflicting. One recent study found that caregivers' perceptions of health-related quality of life (HRQOL) improved 1 year after spine fusion in patients with CP but regressed back to baseline after 2 years and found no change in caregiver burden [41]. However, another study found that spine fusion led to significant improvement in HRQOL, which was maintained at 5 years after surgery [42]. In addition, the authors noted that the substantial complication rate did not correlate with HRQOL changes, arguing that the benefits of surgery outweigh the risks in patients with CP.

Another commonly seen orthopedic problem in patients with CP is hip displacement (subluxation or dislocation), which is known to affect one-third of patients with CP overall. However, the risk of hip displacement has been shown to be linearly related to GMFCS level, reaching as high as 90% in patients with GMFCS level V involvement [27]. In contrast, the risk of hip displacement does not have any relationship to the type of movement disorder. The etiology of hip displacement in CP is

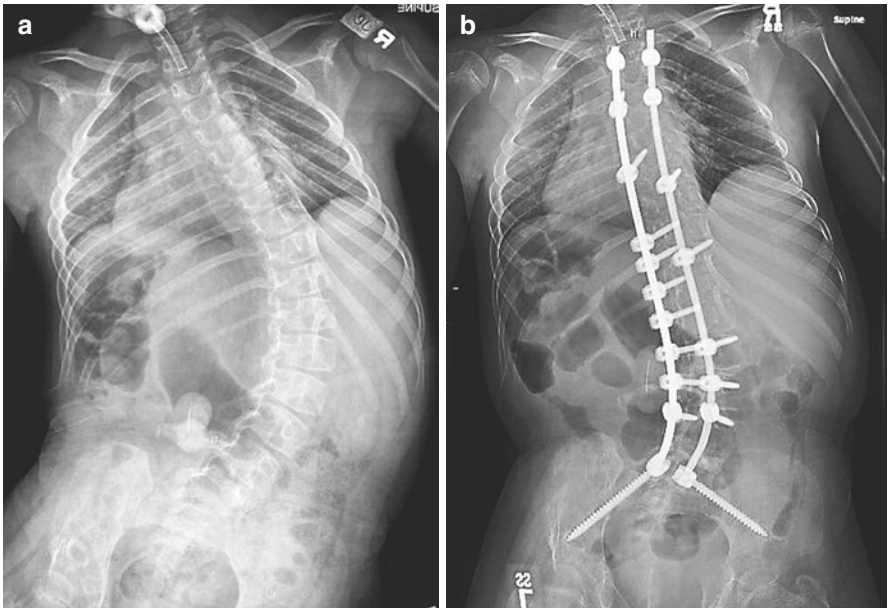


Fig. 52.5 (**a**) Anteroposterior spine radiograph of an 11-year-old tracheostomy-dependent female with GMFCS level V spastic quadriplegia and severe scoliosis. Note the marked pelvic obliquity, which was limiting her sitting ability. (**b**) Postoperative anteroposterior spine radiograph after undergoing posterior spine fusion with segmental instrumentation. Note the concomitant improvement in pelvic obliquity

multifactorial and involves persistence of immature hip morphology, both coxa valga (high femur neck-shaft angle) and femoral anteversion, spasticity of the hip adductor and flexor muscles, and weakness of the hip extensor and abductor muscles. In all patients with CP, hip surveillance is critical to allow early identification of hip subluxation and intervention to prevent dislocation (see Radiographic Studies/Testing/Evaluation section). Untreated hip displacement leads to clinically significant pain in well over 50% of patients [20, 43], difficulty with sitting balance and perineal care, and decreased HRQOL [44]. However, hip surveillance and access to surgery have been associated with improved hip morphology at skeletal maturity and less pain [43].

The goal of orthopedic management of hip displacement is early detection of progressive subluxation and prevention of dislocation. Nonsurgical means have not proved effective in preventing progressive hip displacement. Two randomized controlled trials have demonstrated that botulinum toxin injection and hip abduction bracing may delay the progression of hip displacement but do not prevent the need for surgery [45, 46]. Rather, if detected early enough, simple soft-tissue surgery, typically surgical release or lengthening of the hip adductors and/or hip flexors, may be successful at halting the progression of displacement. Various factors have been shown to influence the success of soft-tissue surgery alone including GMFCS level [47] and degree of hip displacement [48]. Overall, the success of soft-tissue surgery is far from a guarantee. However, even in those cases where soft-tissue surgery delays, rather than prevents, further hip subluxation, there is a benefit. It is well

established that recurrence after bony reconstructive surgery is diminished with increasing patient age. As such, families should be counseled about realistic outcome expectations after soft-tissue surgery and that bony reconstruction may still be needed in the future.

When bony reconstructive surgery is deemed necessary, a one-stage approach is the standard of care (Fig. 52.6), addressing both soft-tissue and bony abnormalities in one setting [49]. Typically, this entails lengthening of the hip adductors combined

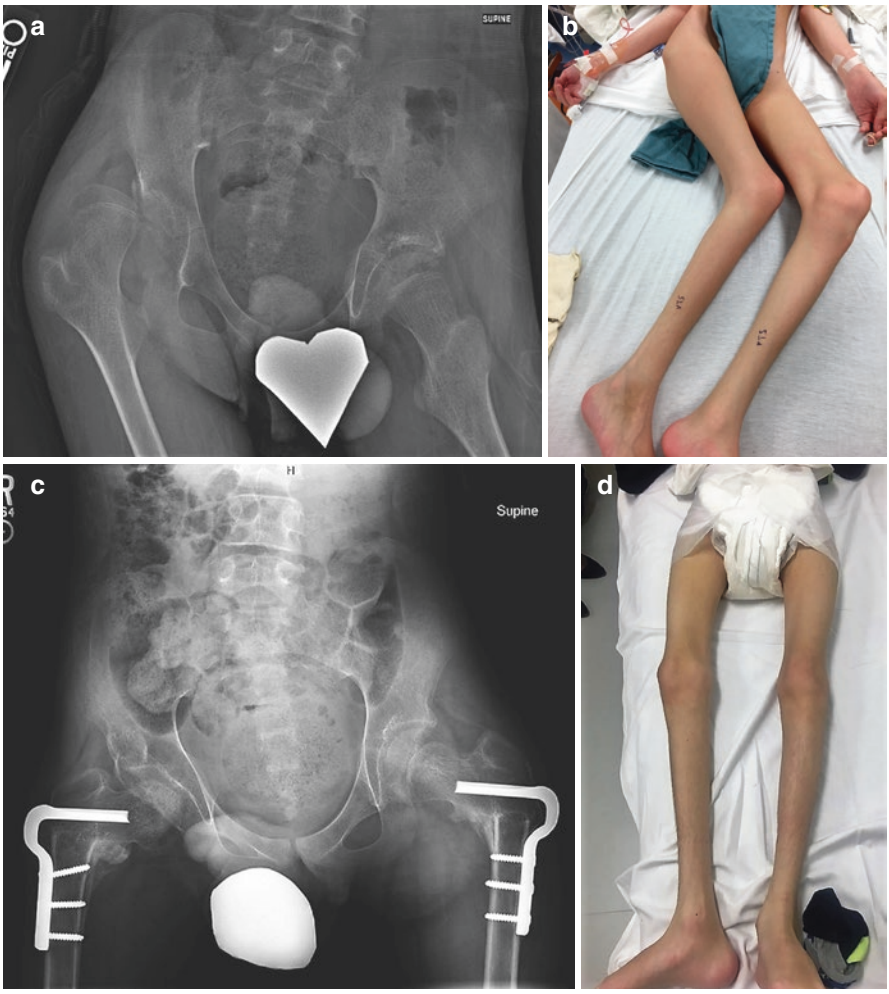


Fig. 52.6 (**a**) Anteroposterior pelvis radiograph of a 14-year-old male with GMFCS level V spastic quadriplegia demonstrates right-hip dislocation. The patient was a recent refugee immigrant and presented with windblown positioning of the lower extremities, seen in (**b**), with pain in right hip and decline in sitting tolerance. (**c**) Postoperative anteroposterior pelvis radiograph taken 6 months after undergoing hip reconstruction. Note the improved coverage of right-hip joint and correction of bilateral coxa valga and right acetabular dysplasia. (**d**) Postoperative clinical photograph showing dramatic improvement in resting posture of the lower extremities. Pain had resolved

with varus, derotation, and shortening osteotomy of the proximal femurs and a pelvic osteotomy. Bony surgery for hip displacement in CP has a high success rate in terms of long-term stability of the hip [46, 48–50] and significant improvement in pain intensity and frequency [51]. In addition, a recent prospective cohort study demonstrated that hip-reconstructive surgery improves HRQOL of nonambulatory children with CP [52].

Clinical Pearls

CP is caused by a nonprogressive disturbance in the developing brain leading to permanent, but not unchanging, disorders in the development of movement, tone, and posture.

The most useful recent development in the classification of CP has been the creation of the Gross Motor Function Classification System (GMFCS), a five-level grading system based on self-initiated movement emphasizing function with regard to sitting and walking. Increase in GMFCS level has been shown to correlate with increased risk of a number of orthopedic comorbidities including scoliosis and hip displacement.

Functional limitation in movement can arise from spasticity and/or contracture. Spasticity may be addressed by nonsurgical methods such as oral medication and botulinum toxin or surgical methods such as intrathecal baclofen or selective dorsal rhizotomy. When contractures are present, options to improve motion include serial casting or orthopedic surgical treatment.

In ambulatory patients, surgery to address lever-arm dysfunction and gait abnormalities should be considered. Computerized gait analysis can be useful in the evaluation of these conditions, including femoral anteversion, tibial torsion, and pes planovalgus, as well as in determining appropriate surgical treatment options.

Scoliosis is common in patients with CP. Spinal fusion requires careful individualized consideration given the known high complication rates.

Hip surveillance is a critical component of the management of every child with CP since hip dislocation is common and preventable through early identification and intervention. Hip surveillance has been shown to alter treatment outcomes, decrease the number of reconstructive surgeries required, and avoid the need for salvage surgery [22].

References

1. Rosenbaum P, Paneth N, Leviton A, Goldstein M, Bax M, Damiano D, et al. A report: the definition and classification of cerebral palsy April 2006. Dev Med Child Neurol Suppl. 2007;109:8–14.
2. Kerr Graham H, Selber P. Musculoskeletal aspects of cerebral palsy. J Bone Joint Surg Br. 2003;85(2):157–66.

3. Graham HK, Rosenbaum P, Paneth N, Dan B, Lin J-P, Damiano DL, et al. Cerebral palsy. Nat Rev Dis Primers. 2016;2:15082.
4. Paneth N, Hong T, Korzeniewski S. The descriptive epidemiology of cerebral palsy. Clin Perinatol. 2006;33(2):251–67.
5. Bonellie SR, Currie D, Chalmers J. Comparison of risk factors for cerebral palsy in twins and singletons. Dev Med Child Neurol. 2005;47(9):587–91.
6. Nelson KB, Grether JK. Causes of cerebral palsy. Curr Opin Pediatr. 1999;11(6):487–91.
7. Winter S, Autry A, Boyle C, Yeargin-Allsopp M. Trends in the prevalence of cerebral palsy in a population-based study. Pediatrics. 2002;110(6):1220–5.
8. Dammann O, Leviton A. Maternal intrauterine infection, cytokines, and brain damage in the preterm newborn. Pediatr Res. 1997;42(1):1–8.
9. Kuban KC, O'Shea TM, Allred EN, Fichorova RN, Heeren T, Paneth N, et al. The breadth and type of systemic inflammation and the risk of adverse neurological outcomes in extremely low gestation newborns. Pediatr Neurol. 2015;52(1):42–8.
10. Reuss ML, Paneth N, Pinto-Martin JA, Lorenz JM, Susser M. The relation of transient hypothyroxinemia in preterm infants to neurologic development at two years of age. N Engl J Med. 1996;334(13):821–7.
11. Collins MP, Lorenz JM, Jetton JR, Paneth N. Hypocapnia and other ventilation-related risk factors for cerebral palsy in low birth weight infants. Pediatr Res. 2001;50(6):712–9.
12. Conde-Agudelo A, Romero R. Antenatal magnesium sulfate for the prevention of cerebral palsy in preterm infants less than 34 weeks' gestation: a systematic review and metaanalysis. Am J Obstet Gynecol. 2009;200(6):595–609.
13. Rouse DJ, Hirtz DG, Thom E, Varner MW, Spong CY, Mercer BM, et al. A randomized, controlled trial of magnesium sulfate for the prevention of cerebral palsy. N Engl J Med. 2008;359(9):895–905.
14. Sotiriadis A, Tsiami A, Papatheodorou S, Baschat AA, Sarafidis K, Makrydimas G. Neurodevelopmental outcome after a single course of antenatal steroids in children born preterm: a systematic review and meta-analysis. Obstet Gynecol. 2015;125(6):1385–96.
15. Jacobs SE, Berg M, Hunt R, Tarnow-Mordi WO, Inder TE, Davis PG. Cooling for newborns with hypoxic ischaemic encephalopathy. Cochrane Database Syst Rev. 2013;(1):CD003311.
16. Novacheck TF, Trost JP, Sohrweide S. Examination of the child with cerebral palsy. Orthop Clin North Am. 2010;41(4):469–88.
17. Ashwal S, Russman BS, Blasco PA, Miller G, Sandler A, Shevell M, et al. Practice parameter: diagnostic assessment of the child with cerebral palsy: report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. Neurology. 2004;62(6):851–63.
18. Reid SM, Dagia CD, Ditchfield MR, Carlin JB, Reddihough DS. Population-based studies of brain imaging patterns in cerebral palsy. Dev Med Child Neurol. 2014;56(3):222–32.
19. Gage JR, DeLuca PA, Renshaw TS. Gait analysis: principle and applications with emphasis on its use in cerebral palsy. Instr Course Lect. 1996;45:491–507.
20. Hagglund G, Alriksson-Schmidt A, Lauge-Pedersen H, Rodby-Bousquet E, Wagner P, Westbom L. Prevention of dislocation of the hip in children with cerebral palsy: 20-year results of a population-based prevention programme. Bone Joint J. 2014;96-B(11):1546–52.
21. Wynter M, Gibson N, Kentish M, Love S, Thomason P, Kerr GH. The consensus statement on hip surveillance for children with cerebral palsy: Australian standards of care. J Pediatr Rehabil Med. 2011;4(3):183–95.
22. Shore B, Spence D, Graham H. The role for hip surveillance in children with cerebral palsy. Curr Rev Musculoskelet Med. 2012;5(2):126–34.
23. Christensen D, Van Naarden BK, Doernberg NS, Maenner MJ, Arneson CL, Durkin MS, et al. Prevalence of cerebral palsy, co-occurring autism spectrum disorders, and motor functioning—Autism and Developmental Disabilities Monitoring Network, USA, 2008. Dev Med Child Neurol. 2014;56(1):59–65.
24. Reid SM, Carlin JB, Reddihough DS. Distribution of motor types in cerebral palsy: how do registry data compare? Dev Med Child Neurol. 2011;53(3):233–8.

25. Palisano R, Rosenbaum P, Walter S, Russell D, Wood E, Galuppi B. Development and reliability of a system to classify gross motor function in children with cerebral palsy. Dev Med Child Neurol. 1997;39(4):214–23.
26. Palisano RJ, Rosenbaum P, Bartlett D, Livingston MH. Content validity of the expanded and revised Gross Motor Function Classification System. Dev Med Child Neurol. 2008;50(10):744–50.
27. Soo B, Howard JJ, Boyd RN, Reid SM, Lanigan A, Wolfe R, et al. Hip displacement in cerebral palsy. J Bone Joint Surg Am. 2006;88(1):121–9.
28. Persson-Bunke M, Hagglund G, Lauge-Pedersen H, Wagner P, Westbom L. Scoliosis in a total population of children with cerebral palsy. Spine (Phila Pa 1976). 2012;37(12):E708–13.
29. Novacheck TF, Gage JR. Orthopedic management of spasticity in cerebral palsy. Childs Nerv Syst. 2007;23(9):1015–31.
30. Andersson C, Mattsson E. Adults with cerebral palsy: a survey describing problems, needs, and resources, with special emphasis on locomotion. Dev Med Child Neurol. 2001;43(2):76–82.
31. Chen YN, Liao SF, Su LF, Huang HY, Lin CC, Wei TS. The effect of long-term conventional physical therapy and independent predictive factors analysis in children with cerebral palsy. Dev Neurorehabil. 2013;16(5):357–62.
32. Dodd KJ, Taylor NF, Damiano DL. A systematic review of the effectiveness of strength-training programs for people with cerebral palsy. Arch Phys Med Rehabil. 2002;83(8):1157–64.
33. Novak I, McIntyre S, Morgan C, Campbell L, Dark L, Morton N, et al. A systematic review of interventions for children with cerebral palsy: state of the evidence. Dev Med Child Neurol. 2013;55(10):885–910.
34. Johnson DC, Damiano DL, Abel MF. The evolution of gait in childhood and adolescent cerebral palsy. J Pediatr Orthop. 1997;17(3):392–6.
35. Bell KJ, Ounpuu S, DeLuca PA, Romness MJ. Natural progression of gait in children with cerebral palsy. J Pediatr Orthop. 2002;22(5):677–82.
36. Rutz E, Donath S, Tirosh O, Graham HK, Baker R. Explaining the variability improvements in gait quality as a result of single event multi-level surgery in cerebral palsy. Gait Posture. 2013;38(3):455–60.
37. Thomason P, Baker R, Dodd K, Taylor N, Selber P, Wolfe R, et al. Single-event multilevel surgery in children with spastic diplegia: a pilot randomized controlled trial. J Bone Joint Surg Am. 2011;93(5):451–60.
38. Thomason P, Selber P, Graham HK. Single Event Multilevel Surgery in children with bilateral spastic cerebral palsy: a 5 year prospective cohort study. Gait Posture. 2013;37(1):23–8.
39. Terjesen T, Lange JE, Steen H. Treatment of scoliosis with spinal bracing in quadriplegic cerebral palsy. Dev Med Child Neurol. 2000;42(7):448–54.
40. Tsirikos AI, Lipton G, Chang WN, Dabney KW, Miller F. Surgical correction of scoliosis in pediatric patients with cerebral palsy using the unit rod instrumentation. Spine (Phila Pa 1976). 2008;33(10):1133–40.
41. DiFazio RL, Miller PE, Vessey JA, Snyder BD. Health-related quality of life and care giver burden following spinal fusion in children with cerebral palsy. Spine (Phila Pa 1976). 2017;42(12):E733–E9.
42. Miyanji F, Nasto LA, Sponseller PD, Shah SA, Samdani AF, Lonner B, et al. Assessing the risk-benefit ratio of scoliosis surgery in cerebral palsy: surgery is worth it. J Bone Joint Surg Am. 2018;100(7):556–63.
43. Wawrzuta J, Willoughby KL, Molesworth C, Ang SG, Shore BJ, Thomason P, et al. Hip health at skeletal maturity: a population-based study of young adults with cerebral palsy. Dev Med Child Neurol. 2016;58(12):1273–80.
44. Ramstad K, Jahnsen RB, Terjesen T. Severe hip displacement reduces health-related quality of life in children with cerebral palsy. Acta Orthop. 2017;88(2):205–10.
45. Graham HK, Boyd R, Carlin JB, Dobson F, Lowe K, Nattrass G, et al. Does botulinum toxin a combined with bracing prevent hip displacement in children with cerebral palsy and “hips at risk”? A randomized, controlled trial. J Bone Joint Surg Am. 2008;90(1):23–33.

46. Willoughby K, Ang SG, Thomason P, Graham HK. The impact of botulinum toxin A and abduction bracing on long-term hip development in children with cerebral palsy. Dev Med Child Neurol. 2012;54(8):743–7.
47. Shore BJ, Yu X, Desai S, Selber P, Wolfe R, Graham HK. Adductor surgery to prevent hip displacement in children with cerebral palsy: the predictive role of the Gross Motor Function Classification System. J Bone Joint Surg Am. 2012;94(4):326–34.
48. Flynn JM, Miller F. Management of hip disorders in patients with cerebral palsy. J Am Acad Orthop Surg. 2002;10(3):198–209.
49. Mubarak SJ, Valencia FG, Wenger DR. One-stage correction of the spastic dislocated hip. Use of pericapsular acetabuloplasty to improve coverage. J Bone Joint Surg Am. 1992;74(9):1347–57.
50. Owers KL, Pyman J, Gargan MF, Witherow PJ, Portinaro NM. Bilateral hip surgery in severe cerebral palsy a preliminary review. J Bone Joint Surg Br. 2001;83(8):1161–7.
51. Rutz E, Vavken P, Camathias C, Haase C, Junemann S, Brunner R. Long-term results and outcome predictors in one-stage hip reconstruction in children with cerebral palsy. J Bone Joint Surg Am. 2015;97(6):500–6.
52. DiFazio R, Shore B, Vessey JA, Miller PE, Snyder BD. Effect of hip reconstructive surgery on health-related quality of life of non-ambulatory children with cerebral palsy. J Bone Joint Surg Am. 2016;98(14):1190–8.

Index

J. F. Sarwark, R. L. Carl (eds.), *Orthopaedics for the Newborn and Young Child*,
https://doi.org/10.1007/978-3-031-11136-5