13 Assessment of the Dysmorphic Infant

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Most infants are born healthy, and the first clinical assessment usually reveals no physical abnormality. However, for the past 20 years, birth defects have been the leading cause of infant mortality in the United States. Each year, approximately 3 percent of live births, or 120,000 babies, are born with major physical structural defects, and one in five infant deaths is attributed to a birth defect.[1]

Fifty to sixty percent of human congenital anomalies are of unknown etiology, and approximately one third are caused by genetic factors. A smaller percentage of birth defects are the result of chromosomal aberrations, gene mutations, and environmental agents, such as viruses and drugs.[2]

The identification of dysmorphic features during the initial physical examination is a crucial first step in the continuum of care for affected infants. A thorough, systematic approach by a skilled examiner can yield important findings and direct the health care team in providing timely and appropriate care for the infant, as well as resources for parents.

Maternal and Family Histories

A complete maternal medical, gynecologic, and obstetric history should be constructed when evaluating the dysmorphic infant. A history of adverse pregnancy outcomes, including multiple miscarriages and stillbirths, can be an important risk factor. Maternal age should be documented because chromosomal anomalies such as trisomy 21 occur more frequently with advancing maternal age. Pregnancies complicated by medical conditions such as diabetes mellitus or hypertension increase the possibility for fetal physical deformities. Prenatal exposure to teratogens, including medications, infections, chemicals, and illicit drugs, must be documented because certain agents cause specific structural abnormalities and functional diseases to be exhibited in the fetus. Critical periods of fetal development, dosage and duration of exposure to the teratogen, and genotype of the embryo must also be taken into consideration.[2] Results of prenatal testing, including multiple marker serum screening, maternal serum α-fetoprotein testing, chorionic villus sampling, and amniocentesis, should be recorded to identify an increased risk or a confirmed diagnosis of fetal disorders such as neural tube defects and trisomies. Additionally, in 2012, noninvasive blood testing, the MateniT21 PLUS test, was made available to detect increased amounts of chromosomal 13,

18, and 21 material as well as an abnormal number of X or Y chromosomes circulating in a pregnant woman's blood.[3]

A comprehensive maternal and paternal family history is also helpful. A number of congenital anomalies and medical conditions can be inherited and therefore place an infant at risk for developing the disorder. Some of these conditions include spina bifida; hydrocephalus; muscular dystrophy; cleft lip; cleft palate; congenital heart defects; polydactyly; clubfoot; congenital hip dislocation; deafness; blindness; childhood cataracts; cystic fibrosis; dwarfism; polycystic kidney disease; and stomach, bowel, or kidney defects.

There are also genetic disorders that occur more commonly within particular ethnic groups. Descendants of Ashkenazi Jewish or French Canadian ancestors may have an increased risk for Tay Sachs disease, an often fatal disorder marked by degeneration of brain tissue and the maculae of the retinas. Infants of African American ancestry are at an increased risk for inheriting sickle cell disease, a serious condition of red blood cells that are distorted in shape and have a tendency to clump together and occlude blood vessels. Thalassemia, a group of hemolytic anemias, is more prevalent in Mediterranean and Asian populations.

If one or both parents are of Jewish, French Canadian, African American, Mediterranean, or Asian descent or if a medical condition occurs repeatedly in one of the partner's families, the couple may consider genetic testing prior to conceiving a child. If either partner is a carrier for a specific inheritable condition, the significance of the results can then be discussed with the couple's health care provider.

Physical Examination

The newborn infant should have a thorough physical examination within 24 hours of birth. This first examination may reveal more abnormalities than any subsequent routine examination done. First, the family, maternal, pregnancy, and perinatal histories are reviewed. The examination is performed in an area that is warm and quiet with good lighting. A systematic approach should be used. Although the exact examination sequence is not important, a consistent approach ensures that all aspects are evaluated. Assessment of gestational age should be included. Knowledge of gestational age can be important in the interpretation of physical findings, especially in infants who are noted to have intrauterine growth restriction (IUGR).

Appearance and posture

An inspection is made for deformations and obvious malformations. An abnormal facial appearance or other abnormalities in appearance can indicate the presence of a syndrome. The newborn's posture at rest usually reflects intrauterine position, sometimes called the *position of comfort*.

Skin

The skin is inspected for abnormalities. Areas of abnormal pigmentation, congenital nevi, hemangiomas, macular stains, or other unusual lesions should be noted.

Head

The shape and size of the head are inspected. The presence of abnormal hair, lacerations, abrasions or contusions, scalp defects, unusual lesions, or protuberances should be noted. An asymmetric skull that persists for longer than two to three days after birth or a palpable ridge along a suture line is abnormal and suggests craniosynostosis. Although occurring in normal infants, craniotabes can be a pathologic finding with syphilis and rickets.

A large anterior fontanel may be associated with congenital hypothyroidism, achondroplasia, hypophosphatasia, chromosomal abnormalities such as Down syndrome, and with IUGR.[4]

Neck

The neck is assessed for masses, decreased mobility, and abnormalities. Cystic hygroma, the most common lymphatic malformation in children, typically presents as a painless mass superior to the clavicle that transilluminates. Redundant skin in the neck may be a feature of some genetic syndromes. Examples include Turner syndrome, in which the neck appears webbed due to redundant skin along the posterolateral line, and Down syndrome, with excess skin posteriorly at the base of the neck.

FIGURE 13-1 ▲ Ear placement.

From: Haldeman-Englert, CR, Saitta SC, and Zackai EH. 2012. Evaluation of the dysmorphic infant. In *Avery's Diseases of the Newborn,* 9th ed., Gleason CA, and Devaskar SU, eds. Philadelphia: Saunders, 189. Reprinted by permission.

Face

The face is examined for symmetry. Facial palsies and asymmetric crying facies are most obvious when the newborn is crying and may go unnoticed in the sleeping or quiet infant. Asymmetric crying facies are the result of hypoplasia or congenital absence of the depressor anguli muscle. Only the muscles controlling movement of one side of the mouth are affected, causing asymmetry of the face with crying. However, the muscles controlling movement of the upper face are normal; so when the infant cries, the forehead wrinkles and both eyes close normally. Asymmetric crying facies have been associated with other anomalies, particularly those of the cardiovascular system.[5] Facial palsy may also be secondary to nerve compression during delivery, which can occur as a result of forceps-assisted delivery.

Eyes

If spacing appears abnormal, the distance between eyes can be measured and compared to standard values (see Figure 5-15). This part of the examination is especially important if other dysmorphic features that suggest a syndrome are present. The presence of epicanthal folds is rarely a normal finding and usually suggests a syndrome (trisomy 21). The sclerae should be clear and white. If the sclerae appear deep blue, osteogenesis imperfecta should be considered. Glaucoma is manifested by a large cloudy cornea. Defects in the iris, such as coloboma, should be noted. Cataracts or retinoblastomas will present as a white pupil when the red reflex is assessed.

Ears

The ears are in normal position when the helix is intersected by a horizontal line drawn from the outer canthus of the eye perpendicular to the vertical axis of the head (Figure 13-1).[6] If the helix falls below this line, the ears are

FIGURE 13-2 ▲ Cryptorchidism.

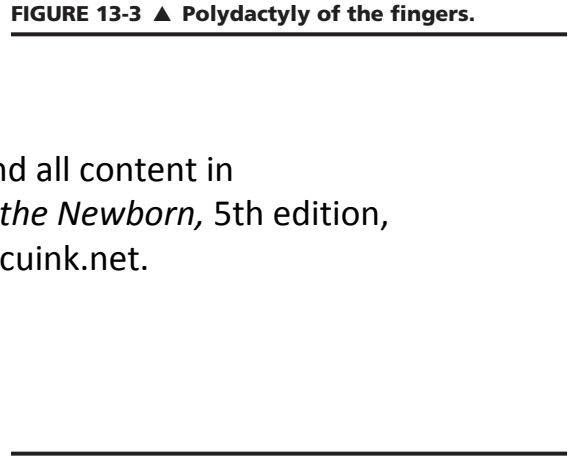


FIGURE 13-3 ▲ Polydactyly of the fingers.

Courtesy of Presbyterian/St. Luke's Medical Center, Denver, Colorado.

Courtesy of Presbyterian/St. Luke's Medical Center, Denver, Colorado.

low set. An ear is posteriorly rotated if its vertical axis deviates more than ten degrees from the vertical axis of the head. Malformations of the external ear are often associated with syndromes of multiple congenital anomalies that include renal malformations. The abnormalities may also indicate additional anomalies of the middle and inner ear associated with hearing loss.

Nose and Mouth

A depressed nasal bridge or an extremely thin or unusually broad nose may occur in some malformation syndromes. Clefts of the soft or hard palate are visible to inspection. Palpation may be needed to detect a submucosal cleft. Macroglossia, or enlargement of the tongue, can be seen with Beckwith-Wiedemann syndrome.

Chest

The chest is examined for size, symmetry, and structure. A malformed or small thorax may be the result of pulmonary hypoplasia or neuromuscular disorders. Pectus excavatum or pectus carinatum may occur as isolated findings or as part of congenital syndromes. Breast size and position should be noted, because widely-spaced nipples occur with some genetic syndromes.

Abdomen

Asymmetry caused by congenital anomalies or masses may first be appreciated by observation. Abnormal, absent, or misplaced kidneys are assessed by using deep palpation (see Figures 9-2 and 9-3). Most abdominal masses in newborns are enlarged kidneys caused by hydronephrosis or cystic renal disease.[4,7] A single umbilical artery is present in 0.3 percent of neonates, occurring more frequently in small for gestational age (SGA) infants, premature infants, and twins.[8] Approximately 40 percent of infants with a single umbilical artery have other major congenital anomalies, predominantly involving the genitourinary system, and have significant mortality. Bourke and colleagues found that in an otherwise normal infant, a single umbilical artery is associated with asymptomatic renal abnormalities in 7 percent of cases.[9,10]

Genitalia

The genitalia are inspected immediately after birth to identify the infant's gender.

FIGURE 13-4 ▲ Polydactyly of the toes.

Courtesy of Presbyterian/St. Luke's Medical Center, Denver, Colorado.

FIGURE 13-5 ▲ Clubfoot.

Courtesy of Presbyterian/St. Luke's Medical Center, Denver, Colorado.

Females

The labia minora should be separated to detect whether the hymen, which normally has some opening, is imperforate. Enlargement of the uterus resulting from an imperforate hymen may be detected as a low midline abdominal mass.

Males

Hypospadias, ventral location of the meatus on the penis, is relatively common. The meatus may be located anywhere from the proximal glans to the perineum, with more severe cases having a more proximal meatus. Infants with perineal or scrotal hypospadias and those with hypospadias of any location accompanied by nonpalpable testes should be evaluated for intersex conditions, including congenital adrenal hyperplasia. Epispadias, dorsal location of the meatus, is uncommon and usually associated with bladder exstrophy.

Ambiguous Genitalia

Signs of ambiguous genitalia include an enlarged clitoris, fused labial folds, and palpable gonads in a phenotypic female and bifid scrotum, severe hypospadias, micropenis, and cryptorchidism (undescended testes) (Figure 13-2) in a phenotypic male. These conditions may be caused by abnormalities of sexual differentiation or congenital adrenal hyperplasia. Infants should be evaluated promptly and the appropriate gender assigned as soon as possible.

Anus

The anus and rectum should be checked carefully for patency, position, and size. Occasionally, large fistulas are mistaken for a normal anus, but if one checks carefully, it will be noted that a fistula will be either anterior or posterior to the usual location of a normal anus.[4,11]

Extremities

The extremities are examined for deformities and movement. The hands and feet are inspected for syndactyly (fusion of digits) and polydactyly (extra digits) (Figures 13-3 and 13-4). Syndactyly and polydactyly can be normal variants in a newborn with an otherwise normal examination, may be associated with a strong family history, or may be associated with various syndromes. The presence of a single palmar crease, or simian crease, should be noted. A single palmar crease occurs in 5–10 percent of the normal population and

FIGURE 13-6 ▲ Constriction defect from amniotic band.

Courtesy of J. Hernandez, MD, The Children's Hospital, Denver, Colorado.

is common in newborns with trisomy 21. Talipes equinovarus (clubfoot) (Figure 13-5) is more common in males. The foot is turned downward and inward, and the sole is directed medially. If position can be corrected with gentle force, it will resolve spontaneously. If not, orthopedic treatment and follow-up are necessary. The hips should be examined to detect developmental dysplasia of the hip.[4]

Trunk and Spine

A tuft of hair, discoloration, or hemangioma in the sacrococcygeal area may suggest an underlying vertebral anomaly. Soft-tissue masses along the spine that are covered with normal skin may be lipomas or myelomeningoceles. A dimple without a visible base may indicate the presence of a pilonidal sinus or tract to the spinal cord.

Sharing Findings with Parents

When an anomaly is identified on physical examination, the infant should be shown to the parents as soon as possible. The physical finding may have been identified antenatally by ultrasound or may not have been expected. Either way, a spectrum of emotional responses from the parents is to be anticipated. Common responses of parents include guilt, intense grief, anger, denial, frustration, and a sense of isolation.[12] It is important to be sensitive to what the parents may be feeling. The defect should be shown to the parents and a factual description given, avoiding opinions or guesses. Genetic counseling should be provided to help parents answer any questions regarding the prognosis for the child and genetic risks for future pregnancies. Medical geneticists and genetic counselors have extensive knowledge of genetic disorders and congenital anomalies and are trained to provide families with psychological and emotional support. However, even a health care professional with a basic knowledge of genetics and Mendelian inheritance can be helpful when discussing the physical findings with the parents and can provide answers to general questions.

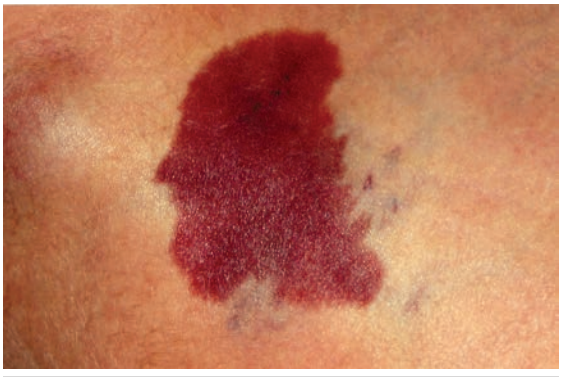
Problems in Morphogenesis

Dysmorphology is the study of congenital anomalies that alter the shape of one or more parts of the body of a newborn child.[13] A congenital anomaly is a structural defect, present at birth, a deviation from normal. Every structural defect represents an inborn error in morphogenesis (development). Minor anomalies are unusual morphologic features that have no serious medical or cosmetic consequences to the patient. Almost any minor defect may occasionally be found as an unusual feature in a particular family. Minor external anomalies are most common in areas of complex and variable features, such as the face, ears, hands, and feet. Clinical diagnosis cannot usually be made based on a single defect. A specific diagnosis most often depends on recognition of an overall pattern of anomalies. Single minor anomalies are present in about 14 percent of newborns; 90 percent of infants with three or more minor anomalies also have one or more major anomaly, requiring significant surgical

FIGURE 13-7 ▲ Amniotic bands resulting in finger amputation.

From: Clark DA. 2000. *Atlas of Neonatology.* Philadelphia: Saunders, 23. Reprinted by permission.

FIGURE 13-8 ▲ Hemangioma.



or cosmetic intervention.[2] Therefore, recognition of both minor and major anomalies is equally important.

Patterns of anomalies can be classified, based on the developmental process involved in their formation, into four categories: malformation, deformation, disruption, and dysplasia. A malformation is a primary structural defect of an organ or larger region of the body resulting from an intrinsically abnormal developmental process.[14,15] Malformations arise from intrinsic defects in genes that specify a series of developmental steps.[13] A malformation in one part of the body is often, but not always associated with malformations elsewhere. Examples of malformations are congenital heart defects or neural tube defects. Malformations occur in all gradations, the manifestations ranging from nearly normal to more severe, and have a recurrence risk of 1–5 percent.[16]

Deformation is an alteration in form, shape, and/or position of a normally formed body part by biomechanical forces that distort the normally developing structure.[14,15] It usually occurs in the fetal period, not in embryogenesis, and is a secondary defect. Congenital hip dislocation and clubfoot are examples of deformations that can be caused by intrauterine constraint. Most deformations apparent at birth either resolve spontaneously or can be treated using external fixation devices to correctly position the affected part. Most deformations have a very good prognosis with a very low recurrence risk.

Disruptions result from an extrinsic insult or destruction of originally normal fetal tissue.[13,15] It is a secondary malformation. Usually, a body part rather than a specific organ is affected. Such disruptions may be vascular, infectious, or mechanical in origin. One example of this is disruption of normally developing tissues by amniotic bands (Figures 13-6 and 13-7).[13] Disruptions are more difficult to treat than deformations because they involve actual loss of normal tissue. Disruptions are generally sporadic with a low recurrence risk.

Dysplasia is a primary defect involving abnormal organization or differentiation of cells into tissue that results in clinically apparent structural changes.[13,15] This can be localized, for example, a hemangioma (Figure 13-8), or generalized, such as achondroplasia (dysplasia of skeletal tissue). Dysplasias are usually not correctable, and the affected

FIGURE 13-9 ▲ Trisomy 21 (Down syndrome).

Typical facies and significant decrease in tone.

Courtesy of J. Hernandez, MD, The Children's Hospital, Denver, Colorado.

individual experiences the clinical effects of the underlying cell or tissue abnormality for life.[17] Malformations and dysplasias are primary events in embryogenesis; disruptions and deformations occur secondarily. The concepts of malformation, deformation, disruption, and dysplasia are useful clinically to assist in recognition, diagnosis, and treatment of congenital anomalies. However, given the constellation of congenital anomalies, a neonate may present with combinations of these patterns of anomalies. The occurrence of congenital anomalies can further be divided into several categories: syndromes, sequences, associations, and teratogenic.

Genetics

The nucleus of the human cell contains chromosomes, structures that include DNA and transmit genetic information during cell division and human development. Each human being has 46 chromosomes—22 pairs of autosomes and a pair of sex chromosomes (XX or XY) that determine gender. The chromosomes contain genes, the biologic units of inheritance. Genes control the physical, biochemical, and physiologic traits passed along to children from their parents. Genetic abnormalities are divided into three categories. Those that:[18]

- influence gene dosage (chromosomal abnormalities such as trisomies)
- involve mutations in the genes themselves (over 6,000 rare single-gene disorders)
- create a vulnerability to developmental errors that are then influenced by environmental factors (multifactorial inheritance disorders such as isolated malformations or schizophrenia)

The gene mutations that cause greater than 6,000 individually rare disorders can be further classified into four categories: autosomal dominant, autosomal recessive, X-linked, and mitochondrial mutations. Each individual receives two sets of chromosomes, one from each parent. Each pair of chromosomes contains a pair of genes, or alleles, that normally work together. A mutant gene is one that has altered in such a way that it can produce an abnormal trait.

Diseases caused by autosomal dominant genes are rare. A single mutant gene is dominant if it masks the effect of its paired gene and causes an obvious abnormality. The risk of the single mutant gene being passed on is 50 percent, but autosomal dominant disorders have a wide range of expression and will present in varying degrees between affected individuals due to influences of the normal paired gene as well as the genetic and environmental background of the individual. Examples of autosomal dominant disorders are retinoblastoma and neurofibromatosis.

Autosomal recessive disorders are also rare, although the number of carriers for these diseases can be high. These disorders are inherited from normal parents who both have the same recessive mutant gene. In most cases, both parents of an affected individual are heterozygous carriers of the disease. Typically, one-fourth of

FIGURE 13-10 ▲ Simian crease.

From: Clark DA. 2000. *Atlas of Neonatology.* Philadelphia: Saunders, 31. Reprinted by permission.

their offspring will be normal heterozygotes, one-half will be normal carrier heterozygotes, and one-fourth will be homozygotes who have the disease. An example of an autosomal recessive disease is cystic fibrosis.[19]

Genes located on the sex chromosomes cause X-linked disorders. The Y chromosome does not appear to carry any disease-causing genes. X-linked dominant traits are rare, but X-linked recessive diseases occur more commonly. A single copy of a mutant gene on the X chromosome will be expressed in the male because he has no normal partner gene. His daughters will all be carriers because they will receive his X gene, and his sons will all be normal because they receive his Y gene. Because females receive an X chromosome from each parent, they can be homozygous normal, homozygous for the X-linked disease, or heterozygous. Fifty percent of male offspring of X-linked recessive women will be affected, and 50 percent of her daughters will be carriers. Examples of X-linked disorders are Turner syndrome and Klinefelter syndrome.

Mitochondrial mutation disorders result from insufficient energy production in critical tissues. Most of these disorders present after the child is born, usually with visual loss, seizures, encephalopathy, progressive myopathy, or diabetes. The human egg is the source of mitochondria for all offspring and is therefore inherited only from the mother. Males with disorders caused by mitochondrial mutations have no risk of passing along the disorder to their offspring. Females, however, have a risk that approaches 100 percent. Female offspring of affected women will inherit some abnormal mitochondria, but may not manifest the disease.[18]

Syndromes

A syndrome is a collection of anomalies involving more than one developmental region or organ system or a pattern of multiple anomalies thought to be pathogenetically related.[17] Chromosomal syndromes are the malformation syndromes usually diagnosed in the neonatal period. The most common of these are trisomy 21, trisomy 18, trisomy 13, and 45,X. With the advent of the human genome project, more information is now available regarding chromosome structure. Once thought to be associations, DiGeorge and Beckwith-Wiedemann have now been found to have chromosomal abnormalities as an underlying etiology and are more correctly categorized as syndromes.

Trisomy 21 (Down Syndrome)

The incidence of trisomy 21 is 1/650–1,000 live births, making it the most common pattern of malformation in man.[20] Down syndrome can usually be diagnosed at birth or

FIGURE 13-11 ▲ Trisomy 18.

A. Prominent occiput; short sternum; micrognathia; malformed, low-set ears. **B.** Overlapping fingers.

Courtesy of J. Hernandez, MD, The Children's Hospital, Denver, Colorado.

soon after by its dysmorphic features that produce a distinctive phenotype. Principal features include hypotonia, poor or absent Moro reflex, hyperextensibility of joints, excess skin at the nape of the neck, flat facial profile (Figure 13-9), low-set ears, slanted palpebral fissures, and single transverse palmar (simian) creases (Figure 13-10). Associated anomalies include congenital heart defects (30–40 percent); increased incidence of duodenal atresia, esophageal atresia, and imperforate anus; and significant hearing loss (90 percent). Most of the features of trisomy 21 can occur as isolated features in normal infants. It is the combination of features forming a recognizable pattern that permits early diagnosis.

Trisomy 18 (Edwards Syndrome)

The incidence of trisomy 18 is approximately 1/5,000–7,000 live births.[15] There is a 4:1 preponderance of females to males. The Edwards syndrome phenotype is as distinct as Down syndrome, but because it is less common, it is less likely to be recognized clinically. Trisomy 18 syndrome (Figure 13-11) is highly lethal, with 50 percent mortality within the first several weeks of life. Only 5 percent of affected infants will survive the first year, and they will have severe mental deficiencies.[14] Physical findings include prenatal and postnatal growth deficiency, micrognathia, overlapping digits, complex congenital heart disease, low-set ears, rocker-bottom clubfeet, and generalized hypertonicity. Associated anomalies include tracheoesophageal fistula or esophageal atresia, hemivertebrae, omphalocele, myelomeningocele, and radial dysplasia.

Trisomy 13 (Patau Syndrome)

The incidence of trisomy 13 is approximately 1/10,000 live births.[21] Trisomy 13 (Figure 13-12) is highly lethal with a mean life expectancy of 130 days.[15] This malformation pattern is quite distinguishable and clinically recognizable. Physical findings include oral-facial clefts, microphthalmia or absence of the eyes, low-set ears, rocker-bottom feet, moderate microcephaly, polydactyly, scalp cutis aplasia, and congenital heart disease. Associated anomalies include cleft lip and palate, cystic kidneys, holoprosencephaly, and other severe central nervous system malformations. The identification of multiple midline defects is a way to recognize trisomy 13.

45,X (Turner Syndrome)

The incidence of monosomy X or Turner syndrome is approximately 1/2,500 live-born females.[22] Ninety-five percent of conceptions

FIGURE 13-12 ▲ Trisomy 13.

Bilateral cleft lip and palate, low-set ears, beak nose, and polydactyly.

Courtesy of J. Hernandez, MD, The Children's Hospital, Denver, Colorado.

FIGURE 13-13 ▲ Turner syndrome.

Lymphedema (hands), webbed neck, low posterior hair line, low-set ears

Courtesy of J. Hernandez, MD, The Children's Hospital, Denver, Colorado.

are miscarried or stillborn. The 45,X syndrome (Figure 13-13) is usually compatible with survival if the fetus reaches term gestation. Females with Turner syndrome can often be identified at birth or before puberty by their distinctive phenotypic characteristics. Physical findings include small stature, short webbed neck, lymphedema of the hands and feet, frontal prominence, low posterior hairline, and broad chest with widely-spaced nipples. Associated anomalies include congenital heart defects, structural kidney defects, and gonadal dysgenesis.

DiGeorge Syndrome

DiGeorge syndrome is a chromosomal deletion of 22q11.2 characterized by structural or functional defects of the thymus, conotruncal heart defects, hypoparathyroidism, and secondary hypocalcemia.[14] DiGeorge syndrome is detected in approximately 1/5,000 live births.[15] Symptoms vary from patient to patient. Physical findings of DiGeorge syndrome include cardiac anomalies, usually conotruncal in nature, such as truncus arteriosus or aortic arch anomalies (approximately 75 percent), cleft palate (approximately 70 percent), immunodeficiency due to thymic hypoplasia (approximately 75 percent), and craniofacial features that include microcephaly, abnormally shaped ears, prominent nasal root with bulbous nasal tip, and hooded eyelids. However, some neonates have no identifying craniofacial features. Associated findings include renal anomalies, hearing loss, significant feeding problems, and hyperextensibility of hands and fingers. Hypocalcemia is a

FIGURE 13-14 ▲ Constraint deformities.

A. Secondary to Potter sequence: narrow, flared thorax, folded ear. **B.** Typical Potter facies: flattened nose, ear anomalies, furrowed brow.

Courtesy of J. Hernandez, MD, The Children's Hospital, Denver, Colorado.

prominent laboratory finding secondary to absence or hypoplasia of the parathyroid glands and thymus. Etiology has been associated with prenatal exposure to alcohol and isotretinoin (Accutane). There is significant neonatal morbidity and mortality associated with the cardiac defects, immunodeficiency, and seizures related to hypocalcemia.

Beckwith-Wiedemann Syndrome

Beckwith-Wiedemann syndrome is caused by a mutation or deletion within the chromosome 11p15.5 region. An estimated 1/13,700 newborns are affected. Beckwith-Wiedemann syndrome is usually identifiable at birth because the infant will be large for gestational age, and have refractory hypoglycemia, a large tongue, creases on the earlobe, and an omphalocele. Hyperplasia of a limb or one side of the face or trunk may be present at birth. Classified as an overgrowth syndrome, affected infants are considerably larger than normal (macrosomia) and continue to grow and gain weight at an unusual rate during childhood. Associated anomalies include renal malformations and cardiomyopathy. Polyhydramnios and a high incidence of prematurity are also common historical findings. Early diagnosis and aggressive treatment of hypoglycemia may prevent mental deficits.

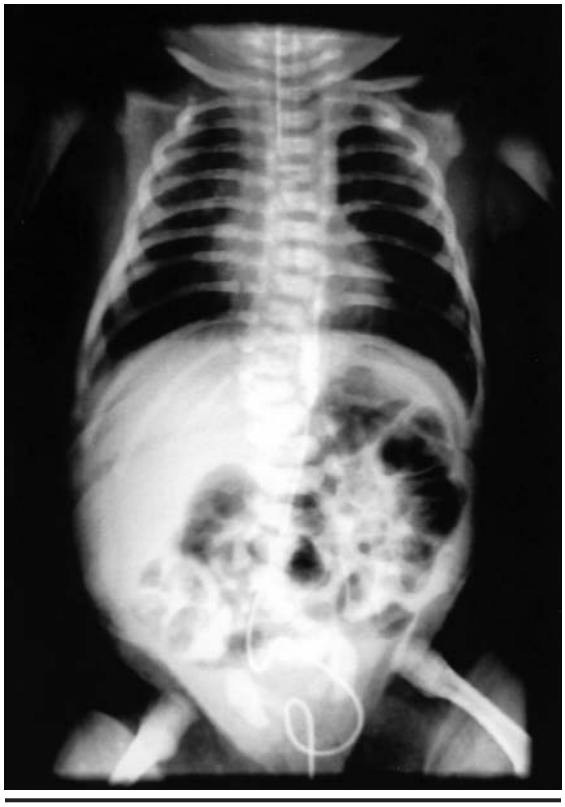
CHARGE Syndrome

CHARGE syndrome is an acronym for **c**oloboma, **h**eart anomaly, choanal **a**tresia, **r**estricted growth and development, **g**enital anomalies, **e**ar anomalies and/or deafness caused by mutations on the CHD7 gene located on chromosome 8q12 (OMIM). Not all features need be present, and the extent of involvement of each system is widely variable.[17] CHARGE syndrome is diagnosable when three or four major criteria or two major and three minor criteria are present. Occurrence of CHARGE syndrome is 1/12,000 live

FIGURE 13-15 ▲ Scoliosis.

To see this and all content in *Physical Assessment of the Newborn,* 5th edition, go to nicuink.net.

FIGURE 13-16 ▲ X-ray of scoliosis.



Courtesy of Presbyterian/St. Luke's Medical Center, Denver, Colorado.

births.[23] CHARGE syndrome often presents as a medical emergency because of the presence of choanal atresia, serious heart defects, and swallowing difficulties. Associated anomalies include cleft lip and palate as well as unilateral facial palsies. Most patients have some degree of mental deficiency or central nervous system defect and visual or auditory anomalies that further compromise cognitive function.

Sequences

A sequence is a pattern of multiple anomalies derived from a single known or presumed structural defect or mechanical factor followed by a cascade of secondary effects.[15] The most common nonchromosomal deformation or disruption sequences diagnosed in the neonatal period are Potter oligohydramnios sequence, amniotic band sequence, arthrogryposis, and Pierre Robin sequence.

Potter Oligohydramnios Sequence

The incidence of Potter sequence is 1/3,000–9,000 live births.[15] Almost all of these infants die in the neonatal period due to pulmonary hypoplasia. Potter sequence is caused by severe oligohydramnios (Figure 13-14). Renal agenesis, polycystic kidneys, urinary tract obstruction, or chronic leakage of amniotic fluid may be the cause of oligohydramnios. This results in intrauterine constraint of the fetus and pulmonary hypoplasia. Physical findings include refractory respiratory distress, frequently with concomitant pneumothoraces, clubfeet, hyperextensible fingers, large ears, low inner eye folds, and a beak nose. Anuria is typically present in the newborn. Associated

TABLE 13-1 ▲ Some Teratogens Known to Cause Human Congenital Anomalies or Birth Defects

Adapted from: Moore KL, Persaud TVN, and Torchia MG. 2013. *The Developing Human: Clinically Oriented Embryology,* 9th ed. Philadelphia: Saunders, 488. Reprinted by permission.

anomalies include congenital heart defects, Eagle-Barrett syndrome (prune belly syndrome [absent abdominal musculature, urinary tract abnormalities, and cryptorchidism]), esophageal and duodenal atresias, imperforate anus, and Pierre Robin sequence. Diagnosis is usually confirmed by renal ultrasound and autopsy findings of urinary tract abnormalities.

Amniotic Band Sequence

The incidence of amniotic band sequence is approximately 1/8,000–11,000 live births.[15] Early amnion rupture occurs, and small bands of amnion encircle developing structures, usually limbs, leading to constrictions, intrauterine amputations, and/or umbilical cord constriction (see Figures 13-6 and 13-7). In addition, deformational defects occur secondary to decreased fetal movement, the result of tethering of a limb by an amniotic band. The decreased fetal movement may result in scoliosis or foot deformities. No two affected fetuses will have the exact same features, and there is no single feature that consistently occurs. Anomalies of the extremities include congenital partial or irregular amputations, constriction rings, and distal swellings. Craniofacial anomalies can include microcephaly, encephaloceles, and facial clefts. Examination of the placenta and membranes is diagnostic.

Arthrogryposis (Multiple Joint Fixations)

Arthrogryposis occurs in approximately 1/8,000 live births.[15] Physical findings include joint contractures, extensions, and dislocations. Joint contractures can be secondary to intrinsic factors affecting the fetus such as early onset of neurologic, muscle, and joint problems or to extrinsic factors such as fetal crowding and constraint. Neurologic abnormality is the most common cause of arthrogryposis. Non–joint-related anomalies may indicate that the arthrogryposis is part of a multiple defect syndrome. Affected infants should also be assessed for scoliosis (Figures 13-15 and 13-16) and hip dislocation.

Pierre Robin Sequence

Pierre Robin sequence occurs in approximately 1/8,500 live births.[15] The initiating defect of this sequence is severe hypoplasia of the mandible causing the tongue to be posteriorly located, resulting in severe upper airway obstruction and cleft palate. Physical findings include micrognathia, cleft palate, and low-set ears. Respiratory distress secondary to upper airway obstruction may be present. Many syndromes have the craniofacial features of Pierre Robin sequence. If noncraniofacial primary malformations are present, then other diagnoses should be considered.

Associations

Association refers to a nonrandom occurrence of multiple malformations for which no specific or common etiology has been identified.[6] The most usual association is VATER/VACTERL.

VATER/VACTERL Association

VATER/VACTERL is an acronym that includes **v**ertebral anomalies, **a**nal atresia, **t**racheo**e**sophageal fistula, and **r**adial and/or **r**enal dysplasia. **C**ardiac defects, single umbilical artery, **l**imb abnormalities, and IUGR are also nonrandom features of this pattern of anomalies. VATER/VACTERL occurs in 1/5,000 live births, and the etiology is unknown.[15] Diagnosis requires exclusion of other similar disorders, including chromosomal syndromes. Most infants diagnosed with VATER/VACTERL have normal brain function and thus merit vigorous attempts toward rehabilitation.

FIGURE 13-17 ▲ Embryonic and fetal development.

From: Moore KL, Persaud TVN, and Torchia MG. 2013. *The Developing Human: Clinically Oriented Embryology,* 9th ed. Philadelphia: Saunders, 489. Reprinted by permission.

Teratogens

Although the human embryo is well protected in the uterus, maternal exposure to teratogens may cause developmental disruptions. A teratogen is any agent external to the fetus that causes a structural or functional disability postnatally. Teratogens can be drugs and chemicals, altered maternal metabolic states, or infectious agents (Table 13-1). Known teratogenic factors cause 5–10 percent of congenital anomalies. Susceptibility to a teratogen is determined by the embryologic stage of development when exposed. Each part, tissue, and organ of an embryo has a critical period during which development can be disrupted (Figure 13-17). The most critical period in development is when cell division, cell differentiation, and morphogenesis are at their peak.

Fetal Alcohol Syndrome

Alcohol is thought to be the most common teratogen to which a fetus may be exposed. The incidence of this disorder in the United States is estimated to be 1–2/1,000 live births.[15] Common features include short palpebral fissures, epicanthal folds, a flat nasal bridge, a long, simple philtrum, a thin upper lip, small hypoplastic nails, irritability in infancy, and growth deficiency. Associated anomalies are cardiac defects, ventricular septal defect being

the most common, and microcephaly. Long-term effects include mental deficiency and behavioral problems.[15,24]

Fetal Cocaine Syndrome

Cocaine is one of the most commonly abused illicit drugs.[13] Infants characteristically are SGA and present with hyperirritability. No definitive physical findings have been established. There is an increased incidence of genitourinary tract anomalies such as hydronephrosis, hypospadias, and Eagle-Barrett syndrome, as well as central nervous system abnormalities such as microcephaly, porencephaly, and infarction that may occur.

Anticonvulsants

Phenytoin (Dilantin) and valproic acid are commonly prescribed for management of maternal epilepsy; however, both are teratogens. Fetal hydantoin syndrome is characterized by a typical facies (broad, low nasal bridge, hypertelorism, epicanthal folds, ptosis, and prominent, malformed ears), low-set hairline, and nail hypoplasia. Cleft lip and palate and umbilical and inguinal hernias are associated anomalies.[15] Fetal valproate syndrome features consist of a prominent or fused metopic suture, epicanthal folds, midface hypoplasia, and broad, low nasal bridge with short nose and long philtrum. Congenital heart defects, genitourinary anomalies, and club feet are associated anomalies.

Infants of Diabetic Mothers

Maternal altered metabolic states can lead to a higher risk for abnormalities in the newborn. Poorly controlled maternal diabetes mellitus with persistent hyperglycemia and ketosis, particularly during embryogenesis, is associated with a two- to three-fold higher incidence of birth defects.[2,15] Infants of diabetic mothers (IDMs) present with anomalies in approximately 1/2,000 births. Common anomalies include holoprosencephaly (failure of the forebrain to divide into hemispheres), meroencephaly (partial absence of the brain), sacral agenesis, vertebral anomalies, congenital heart defects, limb defects, and renal anomalies. Improved diabetic control during gestation dramatically decreases the incidence of diabetes-related malformations, but does not reduce it back to the level of incidence for a mother without diabetes.

Infectious Diseases

Congenital anomalies also may be associated with certain infections during pregnancy. The common and best-understood infections are represented by the acronym TORCH, which stands for **t**oxoplasmosis, **o**ther agents (including syphilis), **r**ubella, **c**ytomegalovirus, and **h**erpes simplex. TORCH infections may present with similar clinical findings: IUGR; hepatosplenomegaly; rash; central nervous system manifestations such as microcephaly, chorioretinitis, and intracranial calcifications; jaundice; and low platelets.

Resources

The World Wide Web is a powerful tool to utilize when searching for information regarding birth defects, including specific conditions, diagnosis, prevention, screening, research, and national organizations. An abundance of reliable and up-to-date information from expert sources can be accessed in a short time. Each of the sources listed below provides links to alternate websites if additional information is desired.

Online Resources for Birth Defect Information

March of Dimes Birth Defects Foundation
http://www.marchofdimes.com/professionals

National Institute of Child Health and Human Development
http://www.nichd.nih.gov

Centers for Disease Control and Prevention
http://www.cdc.gov/ncbddd/birthdefects/index.html

National Newborn Screening and Genetics Resource Center
http://genes-r-us.uthscsa.edu/

The Teratology Society
http://www.teratology.org/

Online Mendelian Inheritance in Man
http://www.ncbi.nlm.nih.gov/omim

Medline Plus
http://www.nlm.nih.gov/medlineplus/birthdefects.html

Gene Tests
http://www.ncbi.nlm.nih.gov

The Genetic Alliance
http://www.geneticalliance.org/

Summary

The approach to the evaluation of the dysmorphic infant is multifaceted and begins with a thorough history and physical examination. With experience, the examiner's identification of physical findings on the continuum of normal to abnormal is enhanced. A general knowledge of genetics and common disorders is helpful when counseling parents. Multiple resources including geneticists, genetic counselors, and Internet websites are available to health care professionals and parents who are involved in providing care to the dysmorphic infant.

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