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Katherine S. Hunt, MS

Genetics and congenital anomalies

Definition

Any unusual variation or abnormality in the shape, structure, and/or function of an organ, body part, or tissue is commonly referred to as a birth defect. However, congenital anomaly is the more accurate and preferred term, since birth defect can be misinterpreted to mean a defect produced by the birthing process. Congenital anomalies may be external or internal, single (isolated) or multiple, major or minor, and by definition are present at (and almost always before) birth, although in some cases detection/diagnosis occurs well after birth. As a group, congenital anomalies are common, have a wide range of clinical severity, and can develop, in one form or another, in any anatomical structure or location. There are many different causes of congenital anomalies, known and unknown, but in terms of how they develop, there are four major types: malformations, deformations, disruptions, and dysplasias.

Description

Variation among individuals in physical characteristics, both external and internal, is an essential attribute of any organism that reproduces sexually, including humans. Although less obvious, but no less important, people also differ in their metabolism and other cellular/chemical processes that help form and maintain the body. The process of normal development in the body is called morphogenesis, while abnormal development is known as dysmorphogenesis. Dymorphology, then, is the study of congenital anomalies, including their formation, causes, and patterns of occurrence.

An important task, in both medical and sociocultural contexts, lies in determining what constitutes a congenital anomaly, and what qualifies as an accepted morphological variant. Further, what distinguishes a major anomaly from a minor one? In other words, what is normal, and what is abnormal? In some cases, the distinction is obvious, in others it is not. Terms such as normal and abnormal are generally agreed to be subjective, and thus not applicable when applied to individuals in a broad context. The same can be said of terms such as defective, anomalous, deformed, malformed, aberrant, irregular,

and the like. Even though some terms and phrases are perceived as subjective, negative, and offensive when misapplied as generalities, they are nonetheless necessary in a medical context. With due sensitivity and care, these same terms can be used clinically in an objective and instructive manner.

Compared with the complex and evolving social issues of perception and acceptance, the medical approach to distinguishing normal variants from minor and major anomalies is more objective and direct. Regardless of the anatomical structure or process, the primary criterion involves evaluating whether its function, shape, structure, and/or size fall within or outside the normal (expected) range. To help answer that question, measurements of every conceivable type have been taken and catalogued over the years on countless individuals. Statistical formulas are applied to the data for a given characteristic or function (e.g., height, weight, blood pressure, serum enzyme levels, etc.) to determine its normal range. If needed, adjustments for age, gender, race, ethnicity, and many other variables can also be made. The results are often graphed and, for most human characteristics, a line drawn through the data points on the graph produces the famous bell curve, a name derived from its shape. Calculations based on such factors as the total number of individuals studied and the range of measurements obtained, among others, are used to mark off a section in the middle of the curve, such that most individuals (usually between 80% and 95%) fall within that range. Therefore, any values above or below (i.e., outside) that range are considered anomalous or abnormal. Measured values for minor anomalies might fall several percentage points on either side of the upper and lower boundaries of the normal range, while major anomalies lie at the ends of the curve.

Among other new challenges, parents and families of children with congenital anomalies are exposed to a bewildering array of new medical terms and phrases, and asked to understand, process, and remember these while likely under a great deal of stress. The practice of medical genetics consists primarily of communicating with individuals and families about difficult and complex issues. Geneticists and genetics counselors are especially sensitive to the psychosocial impact terminology can have on perception and understanding of congenital anomalies/genetic disorders. Parents of a newly diagnosed child inevitably want to know how the anomaly or genetic syndrome occurred. An understanding of the different types of anomalies is the basis for answering that question.

Malformations

A malformation is an abnormality in the shape or structure of an organ, body part, or larger section of the

body resulting from an intrinsically dysfunctional developmental process. In other words, the genetic instructions for development are faulty, interfered with, or both.

All cells in the body carry the same set of genes, copied from the original set provided by the sperm and the egg at conception. Some genes are primarily responsible for directing a portion of embryonic/fetal development, and their influence may be anywhere from general (entire body or entire tissue) to specific (small component of one organ). This is why many single-gene (inherited) and most chromosomal disorders are characterized by multiple major and minor malformations in various anatomic locations. Any disorder, including most with a genetic basis, that can be uniquely characterized by a specific group of anomalies that occur more frequently together in that condition than would be expected by chance is defined as a syndrome. Multiple malformation patterns that have no discernible or consistent genetic pattern or teratogenic cause are known as associations (e.g., **CHARGE association** and **VATER association**).

Most isolated malformations follow a **multifactorial inheritance** pattern, and often involve incomplete morphogenesis of a midline organ or structure (e.g., septal defects (holes) in the heart, cleft lip/palate, diaphragmatic hernia, or **spina bifida**). These same types of malformations occur in some syndromes, in combination with a wide variety of other malformation types. Organs, body parts, or other structures may be extra/missing, abnormally positioned, over developed (hyperplastic), under developed (hypoplastic), or any of a number of minor variations.

Deformations

A deformation is an anomaly in the form, shape, or position of a body part or section that results from mechanical forces on the embryo/fetus. Deformations can have extrinsic (outside the fetus) or intrinsic (internal) causes. Examples of possible extrinsic causes include small maternal stature, oligohydramnios (decreased amniotic fluid volume), breech presentation, uterine malformation, and multiple pregnancy (i.e., twins, triplets, etc.). Some intrinsic (fetal) factors capable of producing deformations include neuromuscular disease, connective tissue defects, central nervous system disorders, and kidney malformations.

Joint contractures, such as talipes equinovarus (clubfoot), are the most common type of deformation, and have both extrinsic and intrinsic causes. As the fetus develops and grows, it must be able to move (flex and extend) the joints or they can become locked in position (contracted). Chronic oligohydramnios produces intrauterine constraint

(IUC), which compresses and immobilizes the fetus, causing joint contractures. Oligohydramnios itself may be caused by leakage of fluid from the amniotic sac (extrinsic cause), or result from decreased fluid production secondary to malformation or absence (agenesis) of the fetal kidneys. (Amniotic fluid is comprised mostly of fetal urine in the later stages of pregnancy.)

Agenesis of the fetal kidneys also exemplifies a malformation/deformation sequence. Specifically, an original, isolated malformation (**renal agenesis**) produces a sequence of events (oligohydramnios plus IUC plus fetal compression) that results in deformations, such as joint contractures and a characteristic facial pattern, which is sometimes referred to as the Potter sequence. A neuromuscular disease that causes partial or total prenatal paralysis of the limbs (decreased mobility) is another example of an intrinsic cause of joint contractures.

Disruptions

A disruption is an anomaly of an organ or body structure resulting from an extrinsic factor that interferes with, or disrupts, an originally normal developmental process. For example, certain types of maternal infection or drug use at a critical time in pregnancy have the potential to arrest the developmental process in specific fetal tissues. Another type of disruption can occur when a strip of the amniotic membrane surrounding the fetus detaches and wraps around one of the developing limbs or a section of the body. Known as an amniotic band, it acts somewhat like a tourniquet, restricting blood flow and inhibiting further growth.

Dysplasias

Dysplasia refers to an abnormal organization of cells in a particular tissue type, and any resulting abnormal morphological development. Dysplasias usually have a genetic basis, and examples include skeletal dysplasias (e.g., fragile, short, and/or abnormally curved bones), ectodermal dysplasias (skin, hair, nails, and associated tissues), and renal dysplasias (multiple cysts or tumors in the kidneys).

Genetic profile

Of all major congenital malformations, 60% have an undetermined cause, and 20% are attributed to multifactorial **inheritance**. The remaining 20% are divided roughly equally between single-gene disorders, chromosomal syndromes, and teratogenic causes. Considering that inclusion in the multifactorial group does not imply a specifically determined cause in any particular case, about 80% of all major malformations have no readily identifiable cause. The most frequently malformed

organs are the brain, heart, and urinary tract (kidneys, ureters, bladder, and urethra). Deformations and disruptions most often affect the extremities (hands and feet), limbs (arms and legs), skull, and face.

Multifactorial inheritance is assumed for most isolated congenital anomalies, with a risk for recurrence in subsequent pregnancies of 3–5%. Single-gene (e.g., autosomal dominant, autosomal recessive, sex-linked, etc.) and chromosomal syndromes present a broad range of recurrence risks, but most often are 1–3% for chromosomal syndromes, and 25% or 50% for single-gene disorders.

Demographics

Considered individually, most anomalies and genetic syndromes are uncommon, and some are quite rare. As a group, however, they are quite common. Major congenital anomalies are the leading cause of death for children less than one year old, and the second and third most frequent cause for those less than five and 15 years old, respectively. Approximately 40% of all pediatric hospital admissions are related to congenital anomalies.

As already noted, malformations may be isolated or multiple, with minor or major clinical significance. Of all newborns, about 14% have a single minor malformation, 3% have a single major malformation, and up to 0.7% have multiple major malformations. The frequency of major malformations is even higher at conception, estimated at 10–15%, but most of these result in spontaneous pregnancy loss. About 2% of newborns are found to have a disruption of some type. In the presence of a major congenital malformation, especially if it affects the central nervous system or urinary tract, there is an 8% risk that a deformation will also occur. Skeletal dysplasias have an overall incidence of about 0.5%, with diagnosis of some of the milder forms often delayed until childhood. Ectodermal dysplasias occur in about 0.7% of individuals, but only several types associated with major malformations are usually diagnosed at birth. Other forms of congenital dysplasias are rare.

Diagnosis

Many anomalies are now detected/diagnosed prenatally, either through testing chosen because of a known or suspected risk factor, as a coincidental finding during testing chosen for another purpose, or as a chance finding by routine prenatal evaluations. Prenatal testing is done either through imaging studies, most often routine (level I) or detailed (level II) obstetric ultrasound, or through direct biochemical or **genetic testing** of the fetus using chorionic villus sampling (CVS) or **amniocentesis**.

Fetal echocardiography is sometimes used to confirm heart defects, and some rare conditions might require x rays or magnetic resonance imaging (MRI) of the fetus (via the mother), while a few others can only be diagnosed by a fetal skin biopsy. Some tests are designed only to screen for certain anomalies or syndromes (increase or decrease the likelihood).

Evaluating congenital anomalies postnatally usually involves attempts to confirm the suspected or most likely diagnosis, while at the same time excluding other possible diagnoses. Major external anomalies are easily detected, but those affecting internal organs require recognition of the signs and symptoms they produce (e.g., a baby with breathing difficulty who turns blue (cyanotic) while crying may have a heart defect), which could be subtle and/or not appear until well after birth.

Any child with an apparently isolated congenital anomaly should have this confirmed (i.e., exclude subtle or hidden signs of an association or syndrome). Multiple congenital anomalies are best evaluated by a geneticist, if possible, even in cases involving an obvious diagnosis, such as a common condition like **Down syndrome**. The family may wish to have a consultation in a genetics clinic, where a comprehensive approach helps to ensure that a thorough evaluation and explanation of the condition are provided. In addition, psychosocial issues are addressed, appropriate referrals can be made (e.g., other specialists, support groups, or more extensive psychological assistance as needed), and the most complete and current information on testing and other options are available. In cases with an unusual presentation of symptoms, or rare syndromes, geneticists have the best chance of establishing a diagnosis, often in consultation with colleagues who specialize in a particular syndrome or class of disorders. In other situations, a geneticist might suggest periodic reevaluations if a diagnosis is unclear initially, since some children grow into a syndrome (i.e., the defining characteristics only become apparent as the child grows). Unfortunately, all too often a diagnosis is never established, regardless of effort expended or specialists consulted. Even in these cases, a geneticist may be able to offer a reasonable estimation as to a cause and recurrence risk, based on a process of eliminating some factors, making others more likely, and applying any available empirical data from similar cases.

Regardless of situation, a genetics evaluation includes as many of the following as possible:

- a complete physical examination of the affected child
- a review of medical records
- evaluation of the pregnancy history
- a consultation to obtain and evaluate the medical history of the immediate and extended family

KEY TERMS

Association—A non-random occurrence in two or more individuals of the same group of anomalies that are not otherwise known to be a sequence or syndrome.

Congenital—Present at birth.

Deformation—Abnormal shape or function in otherwise normal tissue produced by unusual mechanical forces on the embryo/fetus.

Disruption—A type of anomaly formation in which a breakdown or inhibition of normal tissue development occurs.

Dysmorphic—Literally meaning misshapen, it is most often used as a general descriptive term for individuals with one or more anomalous physical characteristics.

Dysplasia—The structural and functional results of the abnormal organization of cells into tissues, affecting one or more of the derivatives of a primary tissue type (endoderm, mesoderm, or ectoderm).

Etiology—The cause of a disease, syndrome, or anomaly.

Idiopathic—One or more anomalies of unknown cause in an individual.

Malformation—An abnormality in an organ or body structure caused by a dysfunctional developmental process.

Morphogenesis—The normal developmental process of the body's structure and form.

Sequence—The combination of both a primary structural or functional anomaly, and the secondary anomalies produced by any abnormal forces or processes it generates.

Syndrome—A pattern of multiple major and minor anomalies that occur as a group more often than would be expected by chance alone, implying the same underlying cause or mechanism in all affected individuals.

Based on these evaluations, one or more of a wide variety of possible medical tests could be suggested. If a hereditary syndrome is suspected, physical examination, medical record review, and testing might also be requested of one or more family members to help establish a diagnosis. The importance of making a diagnosis rests in the ability it provides to answer other questions

parents inevitably have. The diagnostic process also attempts to determine how a malformation, deformation, disruption, dysplasia, or some combination, occurred.

Treatment and management

Deformations are typically more amenable to successful treatment and correction than other types of anomalies. For instance, infants with dislocated hips or clubfeet can usually achieve normal function after a regimen of bracing, casting, and movement therapy, although in some cases minor surgery is also necessary. Many malformations can also be successfully repaired, especially those that are isolated. However, invasive and complex surgery is often needed, with only partial improvement in some cases. Certain malformations, such as cleft lip/palate, require multiple surgeries performed in stages as the child grows. For the most part, disruptions and dysplasias are minimally treatable, if at all. However, an exception could be the use of a prosthetic device for a limb amputation anomaly caused by a disruption such as an amniotic band.

Prognosis

The prognosis for any particular congenital anomaly, whether isolated or part of a sequence or syndrome, can vary greatly. Medical complications from one anomaly may also adversely affect the prognosis of another, or affect the course of an entire syndrome. In general, however, children with extrinsically caused deformations tend to fare better than those with other types of anomalies. Likewise, isolated malformations usually carry a better prognosis than multiple malformations/deformations, intrinsically derived deformations, and most types of tissue dysplasia. Disruption anomalies have widely varying prognoses based on various factors, such as the organ or body parts affected, the degree of disruption, and the timing during morphogenesis at which the disruption began.

Resources

BOOKS

Moore, Keith L., and T. V. N. Persaud. *Before We Are Born: Essentials of Embryology and Birth Defects*, 5th edition. Philadelphia: W. B. Saunders Company, 1998.

PERIODICALS

Riddle, Robert D., and Clifford J. Tabin. "How Limbs Develop." *Scientific American*. 280 (February 1999): 74–79.

ORGANIZATIONS

Alliance of Genetic Support Groups. 4301 Connecticut Ave. NW, Suite 404, Washington, DC 20008. (202) 966-5557.

March of Dimes Birth Defects Foundation. 1275 Mamaroneck Ave., White Plains, NY 10605. (888) 663-4637. (April 19, 2005.) <<http://www.marchofdimes.com>>.

National Society of Genetic Counselors. 233 Canterbury Dr., Wallingford, PA 19086-6617. (610) 872-1192. (April 19, 2005.) <<http://www.nsgc.org/>>.

WEBSITES

Cho, Mike, Mike Cohen, and Seeta Sistla. *What Is a "Normal" Phenotype? A Paper Written as Background to Discussion*. Developmental Biology Online. April 15, 2003 (April 18, 2005). <<http://www.devbio.com/article.php?ch=21&id=169>>.

View Dysmorphic Syndrome Features. Institute of Child Health, University College, London. (April 18, 2004.) <http://www.hgmp.mrc.ac.uk/DHMHD/view_human.html>.

Scott J. Polzin, MS

Genitalia, ambiguous

Definition

Ambiguous genitalia is a congenital anomaly in which the genital organs do not appear to be male or female.

Description

Ambiguous genitalia, also called indeterminate sex and intersexuality, is a condition present at birth in which an individual has what appears to be both male and female external sex organs. This diagnosis is usually preliminary, based on an initial physical examination. After further evaluation and diagnostic procedures, specific genital anomalies are usually diagnosed and the underlying syndrome or condition that caused them identified.

When the genitals are abnormal, a genetic screening is usually performed to determine the genetic sex of the infant and to rule out **chromosomal abnormalities**.

In a genetic female with ambiguous genitalia, the clitoris may be enlarged, having the appearance of a small penis, the labia may be fused, resembling a scrotum, and the opening to the urinary tract may be located anywhere along the clitoris.

In a genetic male with ambiguous genitalia, the penis may be small, measuring less than .78 in (2 cm); it can be mistaken for an enlarged clitoris. The clitoris often appears enlarged in newborns. The testicles may be undescended, a condition in which they remain inside the body, and they may have a groove or cleft resembling labia. The urinary tract opening may be located any-

where from the tip of the penis to any point along the underside, an anomaly known as **hypospadias**.

Ambiguous genitalia is not a medically threatening anomaly, but it can be an extremely emotional issue for parents. Often parents must decide in which gender the child will be raised. This is a complex and difficult decision. There are health care professionals who can help inform and support parents. Counselors, doctors, and surgeons should be consulted before this decision is made.

The assignment of gender is not always based solely on the genetic sex of the child. When surgical treatment is necessary, parents may choose to raise a genetic male as a female because it is easier to surgically create functional female genitalia than male genitalia.

Children with ambiguous genitalia generally have one of the following conditions that cause the external genitalia to be abnormal:

- **Congenital adrenal hyperplasia:** This is the most common cause of ambiguous genitalia in infants. It is a condition affecting only females, in which the fetus cannot process an enzyme called 21-hydroxylase, causing an inability to process steroids in the body. It is characterized by a genetic female with internal female sex organs and ambiguous or masculine external genitalia.
- **True hermaphroditism:** In this extremely rare condition, an individual has both ovarian and testicular tissue, the internal sex organs of both genders, external genitalia that are ambiguous or of both genders, and abnormalities of the X or Y **chromosome**.
- **Pseudohermaphroditism:** In this condition, the individual has ambiguous external genitalia, but the internal sex organs of only one gender.
- **Gonadal dysgenesis:** In this condition, an individual has the internal sex organs of a female, external genitalia that have characteristics of both genders, but are predominantly female, abnormalities of the X or Y chromosome, and poorly developed ovaries or testicles.
- **Klinefelter's syndrome:** This is a chromosomal abnormality in which males have an extra X chromosome. It is characterized by small testicles, infertility, and, in some cases, mental retardation.

Genetic profile

The development of normal genitalia is a complex sequential process, beginning with the information stored on the X and Y chromosomes. Gonadal development in the fetus is first regulated by genetic information found on the short arm of the Y chromosome. Testis-determining