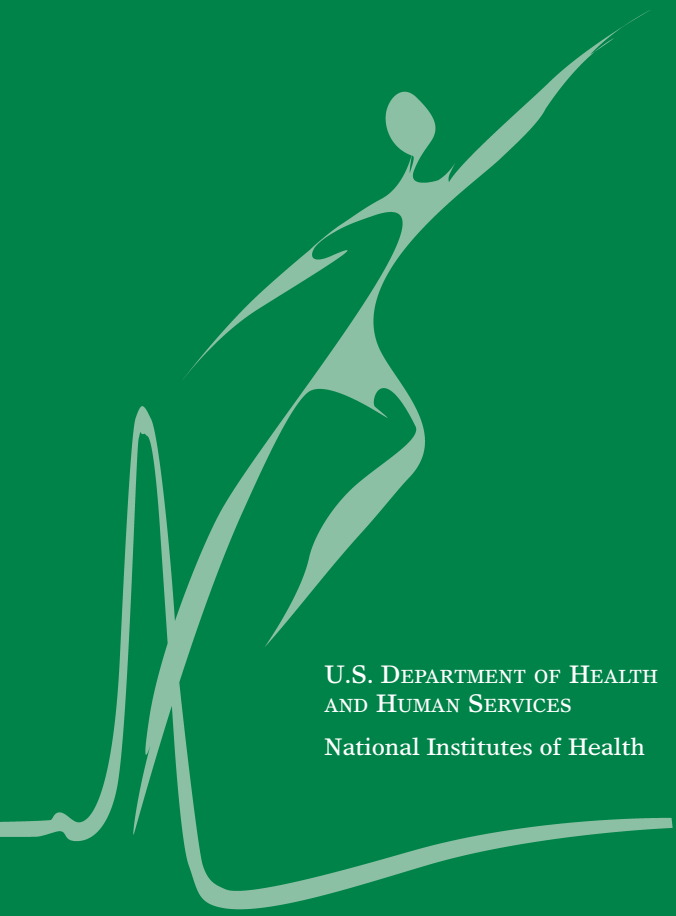
Cephalic Disorders



U.S. Department of Health and Human Services

National Institutes of Health

Cephalic Disorders

What are cephalic disorders?

Cephalic disorders are congenital conditions that stem from damage to, or abnormal development of, the budding nervous system. *Cephalic* is a term that means "head" or "head end of the body." *Congenital* means the disorder is present at, and usually before, birth. Although there are many congenital developmental disorders, this fact sheet briefly describes only cephalic conditions.

Cephalic disorders are not necessarily caused by a single factor but may be influenced by hereditary or genetic conditions or by environmental exposures during pregnancy such as medication taken by the mother, maternal infection, or exposure to radiation. Some cephalic disorders occur when the cranial sutures (the fibrous joints that connect the bones of the skull) join prematurely. Most cephalic disorders are caused by a disturbance that occurs very early in the development of the fetal nervous system.

The human nervous system develops from a small, specialized plate of cells on the surface of the embryo. Early in development, this plate of cells forms the *neural tube*, a narrow sheath that closes between the third and fourth weeks of pregnancy to form the

brain and spinal cord of the embryo. Four main processes are responsible for the development of the nervous system: *cell proliferation*, the process in which nerve cells divide to form new generations of cells; *cell migration*, the process in which nerve cells move from their place of origin to the place where they will remain for life; *cell differentiation*, the process during which cells acquire individual characteristics; and *cell death*, a natural process in which cells die. Understanding the normal development of the human nervous system, one of the research priorities of the National Institute of Neurological Disorders and Stroke, may lead to a better understanding of cephalic disorders.

Damage to the developing nervous system is a major cause of chronic, disabling disorders and, sometimes, death in infants, children, and even adults. The degree to which damage to the developing nervous system harms the mind and body varies enormously. Many disabilities are mild enough to allow those afflicted to eventually function independently in society. Others are not. Some infants, children, and adults die, others remain totally disabled, and an even larger population is partially disabled, functioning well below normal capacity throughout life.

What are the different kinds of cephalic disorders?

ANENCEPHALY is a *neural tube defect* that occurs when the cephalic (head) end of the neural tube fails to close, usually between the 23rd and 26th days of pregnancy, resulting in the absence of a major portion of the brain, skull, and scalp. Infants with this disorder are born without a forebrain—the largest part of the brain consisting mainly of the cerebrum, which is responsible for thinking and coordination. The remaining brain tissue is often exposed—not covered by bone or skin.

Infants born with anencephaly are usually blind, deaf, unconscious, and unable to feel pain. Although some individuals with anencephaly may be born with a rudimentary brainstem, the lack of a functioning cerebrum permanently rules out the possibility of ever gaining consciousness. Reflex actions such as breathing and responses to sound or touch may occur.

The disorder is one of the most common disorders of the fetal central nervous system. Approximately 1,000 to 2,000 American babies are born with anencephaly each year. The disorder affects females more often than males.

The cause of anencephaly is unknown. Although it is believed that the mother's diet and vitamin intake may play a role, scientists agree that many other factors are also involved.

There is no cure or standard treatment for anencephaly and the prognosis for affected individuals is poor. Most infants do not survive infancy. If the infant is not stillborn, then he or she will usually die within a few hours or days after birth. Anencephaly can often be diagnosed before birth through an ultrasound examination.

Recent studies have shown that the addition of folic acid to the diet of women of childbearing age may significantly reduce the incidence of neural tube defects. Therefore it is recommended that all women of childbearing age consume 0.4 mg of folic acid daily.

COLPOCEPHALY is a disorder in which there is an abnormal enlargement of the occipital horns—the posterior or rear portion of the lateral ventricles (cavities or chambers) of the brain. This enlargement occurs when there is an underdevelopment or lack of thickening of the white matter in the posterior cerebrum. Colpocephaly is characterized by microcephaly (abnormally small head) and mental retardation. Other features may include motor abnormalities, muscle spasms, and seizures.

Although the cause is unknown, researchers believe that the disorder results from an intrauterine disturbance that occurs between the second and sixth months of pregnancy.

Colpocephaly may be diagnosed late in pregnancy, although it is often misdiagnosed as hydrocephalus (excessive accumulation of cerebrospinal fluid in the brain). It may be more accurately diagnosed after birth when

signs of mental retardation, microcephaly, and seizures are present.

There is no definitive treatment for colpocephaly. Anticonvulsant medications can be given to prevent seizures, and doctors try to prevent contractures (shrinkage or shortening of muscles).

The prognosis for individuals with colpocephaly depends on the severity of the associated conditions and the degree of abnormal brain development. Some children benefit from special education.

HOLOPROSENCEPHALY is a disorder characterized by the failure of the prosencephalon (the forebrain of the embryo) to develop. During normal development the forebrain is formed and the face begins to develop in the fifth and sixth weeks of pregnancy. Holoprosencephaly is caused by a failure of the embryo's forebrain to divide to form bilateral cerebral hemispheres (the left and right halves of the brain), causing defects in the development of the face and in brain structure and function.

There are three classifications of holoprosencephaly. *Alobar holoprosencephaly*, the most serious form in which the brain fails to separate, is usually associated with severe facial anomalies. *Semilobar holoprosencephaly*, in which the brain's hemispheres have a slight tendency to separate, is an intermediate form of the disease. *Lobar holoprosencephaly*, in which there is considerable evidence of separate brain hemispheres, is the least severe form. In some cases of

lobar holoprosencephaly, the patient's brain may be nearly normal.

Holoprosencephaly, once called *arhinencephaly*, consists of a spectrum of defects or malformations of the brain and face. At the most severe end of this spectrum are cases involving serious malformations of the brain, malformations so severe that they are incompatible with life and often cause spontaneous intrauterine death. At the other end of the spectrum are individuals with facial defects—which may affect the eyes, nose, and upper lip—and normal or near-normal brain development. Seizures and mental retardation may occur.

The most severe of the facial defects (or anomalies) is *cyclopia*, an abnormality characterized by the development of a single eye, located in the area normally occupied by the root of the nose, and a missing nose or a nose in the form of a proboscis (a tubular appendage) located above the eye.

Ethmocephaly is the least common facial anomaly. It consists of a proboscis separating narrow-set eyes with an absent nose and microphthalmia (abnormal smallness of one or both eyes).

Cebocephaly, another facial anomaly, is characterized by a small, flattened nose with a single nostril situated below incomplete or underdeveloped closely set eyes.

The least severe in the spectrum of facial anomalies is the median cleft lip, also called *premaxillary agenesis*.

Although the causes of most cases of holoprosencephaly remain unknown, researchers know that approximately one-half of all cases have a chromosomal cause. Such chromosomal anomalies as Patau's syndrome (trisomy 13) and Edwards' syndrome (trisomy 18) have been found in association with holoprosencephaly. There is an increased risk for the disorder in infants of diabetic mothers.

There is no treatment for holoprosencephaly and the prognosis for individuals with the disorder is poor. Most of those who survive show no significant developmental gains. For children who survive, treatment is symptomatic. Although it is possible that improved management of diabetic pregnancies may help prevent holoprosencephaly, there is no means of primary prevention.

HYDRANENCEPHALY is a rare condition in which the cerebral hemispheres are absent and replaced by sacs filled with cerebrospinal fluid. Usually the cerebellum and brainstem are formed normally. An infant with hydranencephaly may appear normal at birth. The infant's head size and spontaneous reflexes such as sucking, swallowing, crying, and moving the arms and legs may all seem normal. However, after a few weeks the infant usually becomes irritable and has increased muscle tone (hypertonia).

After several months of life, seizures and hydrocephalus may develop. Other symptoms may include visual impairment, lack of growth, deafness, blindness, spastic quadriparesis (paralysis), and intellectual deficits.

Hydranencephaly is an extreme form of porencephaly (a rare disorder, discussed later in this fact sheet, characterized by a cyst or cavity in the cerebral hemispheres) and may be caused by vascular insult (such as stroke) or injuries, infections, or traumatic disorders after the 12th week of pregnancy.

Diagnosis may be delayed for several months because the infant's early behavior appears to be relatively normal. Transillumination, an examination in which light is passed through body tissues, usually confirms the diagnosis. Some infants may have additional abnormalities at birth, including seizures, myoclonus (involuntary sudden, rapid jerks), and respiratory problems.

There is no standard treatment for hydranencephaly. Treatment is symptomatic and supportive. Hydrocephalus may be treated with a shunt.

The outlook for children with hydranencephaly is generally poor, and many children with this disorder die before age 1. However, in rare cases, children with hydrocephalus may survive for several years or more.

INIENCEPHALY is a rare neural tube defect that combines extreme retroflexion (backward bending) of the head with severe defects of the spine. The affected infant tends to be short, with a disproportionately large head. Diagnosis can be made immediately after birth because the head is so severely retroflexed that the face looks upward. The skin of the face is connected directly to the skin of the chest and the

scalp is directly connected to the skin of the back. Generally, the neck is absent.

Most individuals with iniencephaly have other associated anomalies such as anencephaly, cephalocele (a disorder in which part of the cranial contents protrudes from the skull), hydrocephalus, cyclopia, absence of the mandible (lower jaw bone), cleft lip and palate, cardiovascular disorders, diaphragmatic hernia, and gastrointestinal malformation. The disorder is more common among females.

The prognosis for those with iniencephaly is extremely poor. Newborns with iniencephaly seldom live more than a few hours. The distortion of the fetal body may also pose a danger to the mother's life.

LISSENCEPHALY, which literally means "smooth brain," is a rare brain malformation characterized by microcephaly and the lack of normal convolutions (folds) in the brain. It is caused by defective neuronal migration, the process in which nerve cells move from their place of origin to their permanent location.

The surface of a normal brain is formed by a complex series of folds and grooves. The folds are called *gyri* or convolutions, and the grooves are called *sulci*. In children with lissencephaly, the normal convolutions are absent or only partly formed, making the surface of the brain smooth.

Symptoms of the disorder may include unusual facial appearance, difficulty swallowing, failure to thrive, and severe psychomotor retardation. Anomalies of the hands, fingers, or toes, muscle spasms, and seizures may also occur.

Lissencephaly may be diagnosed at or soon after birth. Diagnosis may be confirmed by ultrasound, computed tomography (CT), or magnetic resonance imaging (MRI).

Lissencephaly may be caused by intrauterine viral infections or viral infections in the fetus during the first trimester, insufficient blood supply to the baby's brain early in pregnancy, or a genetic disorder. There are two distinct genetic causes of lissencephaly—X-linked and chromosome 17-linked.

The spectrum of lissencephaly is only now becoming more defined as neuroimaging and genetics has provided more insights into migration disorders. Other causes which have not yet been identified are likely as well.

Lissencephaly may be associated with other diseases including isolated lissencephaly sequence, Miller-Dieker syndrome, and Walker-Warburg syndrome.

Treatment for those with lissencephaly is symptomatic and depends on the severity and locations of the brain malformations. Supportive care may be needed to help with comfort and nursing needs. Seizures may be controlled with medication and hydrocephalus may require shunting. If feeding becomes difficult, a gastrostomy tube may be considered.

The prognosis for children with lissencephaly varies depending on the degree of brain malformation. Many individuals show no significant development beyond a 3- to 5-month-old level. Some may have near-normal development and intelligence.

Many will die before the age of 2. Respiratory problems are the most common causes of death.

MEGALENCEPHALY, also called *macrencephaly*, is a condition in which there is an abnormally large, heavy, and usually malfunctioning brain. By definition, the brain weight is greater than average for the age and gender of the infant or child. Head enlargement may be evident at birth or the head may become abnormally large in the early years of life.

Megalencephaly is thought to be related to a disturbance in the regulation of cell reproduction or proliferation. In normal development, neuron proliferation—the process in which nerve cells divide to form new generations of cells—is regulated so that the correct number of cells is formed in the proper place at the appropriate time.

Symptoms of megalencephaly may include delayed development, convulsive disorders, corticospinal (brain cortex and spinal cord) dysfunction, and seizures. Megalencephaly affects males more often than females.

The prognosis for individuals with megalencephaly largely depends on the underlying cause and the associated neurological disorders. Treatment is symptomatic. Megalencephaly may lead to a condition called *macrocephaly* (defined later in this fact sheet).

Unilateral megalencephaly or *hemimegalencephaly* is a rare condition characterized by the enlargement of one-half of the brain.

Children with this disorder may have a large, sometimes asymmetrical head. Often they suffer from intractable seizures and mental retardation. The prognosis for those with hemimegalencephaly is poor.

MICROCEPHALY is a neurological disorder in which the circumference of the head is smaller than average for the age and gender of the infant or child. Microcephaly may be congenital or it may develop in the first few years of life. The disorder may stem from a wide variety of conditions that cause abnormal growth of the brain, or from syndromes associated with chromosomal abnormalities.

Infants with microcephaly are born with either a normal or reduced head size. Subsequently the head fails to grow while the face continues to develop at a normal rate, producing a child with a small head, a large face, a receding forehead, and a loose, often wrinkled scalp. As the child grows older, the smallness of the skull becomes more obvious, although the entire body also is often underweight and dwarfed. Development of motor functions and speech may be delayed. Hyperactivity and mental retardation are common occurrences, although the degree of each varies. Convulsions may also occur. Motor ability varies, ranging from clumsiness in some to spastic quadriplegia in others.

Generally there is no specific treatment for microcephaly. Treatment is symptomatic and supportive.

In general, life expectancy for individuals with microcephaly is reduced and the prognosis for normal brain function is poor. The prognosis varies depending on the presence of associated abnormalities.

PORENCEPHALY is an extremely rare disorder of the central nervous system involving a cyst or cavity in a cerebral hemisphere. The cysts or cavities are usually the remnants of destructive lesions, but are sometimes the result of abnormal development. The disorder can occur before or after birth.

Porencephaly most likely has a number of different, often unknown causes, including absence of brain development and destruction of brain tissue. The presence of porencephalic cysts can sometimes be detected by transillumination of the skull in infancy. The diagnosis may be confirmed by CT, MRI, or ultrasonography.

More severely affected infants show symptoms of the disorder shortly after birth, and the diagnosis is usually made before age 1. Signs may include delayed growth and development, spastic paresis (slight or incomplete paralysis), hypotonia (decreased muscle tone), seizures (often infantile spasms), and macrocephaly or microcephaly.

Individuals with porencephaly may have poor or absent speech development, epilepsy, hydrocephalus, spastic contractures (shrinkage or shortening of muscles), and mental retardation. Treatment may

include physical therapy, medication for seizure disorders, and a shunt for hydrocephalus. The prognosis for individuals with porencephaly varies according to the location and extent of the lesion. Some patients with this disorder may develop only minor neurological problems and have normal intelligence, while others may be severely disabled. Others may die before the second decade of life.

SCHIZENCEPHALY is a rare developmental disorder characterized by abnormal slits, or clefts, in the cerebral hemispheres. Schizencephaly is a form of porencephaly. Individuals with clefts in both hemispheres, or bilateral clefts, are often developmentally delayed and have delayed speech and language skills and corticospinal dysfunction. Individuals with smaller, unilateral clefts (clefts in one hemisphere) may be weak on one side of the body and may have average or near-average intelligence. Patients with schizencephaly may also have varying degrees of microcephaly, mental retardation, hemiparesis (weakness or paralysis affecting one side of the body), or quadriparesis (weakness or paralysis affecting all four extremities), and may have reduced muscle tone (hypotonia). Most patients have seizures and some may have hydrocephalus.

In schizencephaly, the neurons border the edge of the cleft implying a very early disruption in development. There is now a genetic origin for one type of schizencephaly. Causes of this type may include

environmental exposures during pregnancy such as medication taken by the mother, exposure to toxins, or a vascular insult. Often there are associated heterotopias (isolated islands of neurons) which indicate a failure of migration of the neurons to their final position in the brain.

Treatment for individuals with schizencephaly generally consists of physical therapy, treatment for seizures, and, in cases that are complicated by hydrocephalus, a shunt.

The prognosis for individuals with schizencephaly varies depending on the size of the clefts and the degree of neurological deficit.

What are other less common cephalies?

ACEPHALY literally means absence of the head. It is a much rarer condition than anencephaly. The acephalic fetus is a parasitic twin attached to an otherwise intact fetus. The acephalic fetus has a body but lacks a head and a heart; the fetus's neck is attached to the normal twin. The blood circulation of the acephalic fetus is provided by the heart of the twin. The acephalic fetus can not exist independently of the fetus to which it is attached.

EXENCEPHALY is a condition in which the brain is located outside of the skull. This condition is usually found in embryos as an early stage of anencephaly. As an exencephalic pregnancy progresses, the neural tissue gradually degenerates. It is

unusual to find an infant carried to term with this condition because the defect is incompatible with survival.

MACROCEPHALY is a condition in which the head circumference is larger than average for the age and gender of the infant or child. It is a descriptive rather than a diagnostic term and is a characteristic of a variety of disorders. Macrocephaly also may be inherited. Although one form of macrocephaly may be associated with mental retardation, in approximately one-half of cases mental development is normal. Macrocephaly may be caused by an enlarged brain or hydrocephalus. It may be associated with other disorders such as dwarfism, neurofibromatosis, and tuberous sclerosis.

MICRENCEPHALY is a disorder characterized by a small brain and may be caused by a disturbance in the proliferation of nerve cells. Micrencephaly may also be associated with maternal problems such as alcoholism, diabetes, or rubella (German measles). A genetic factor may play a role in causing some cases of micrencephaly. Affected newborns generally have striking neurological defects and seizures. Severely impaired intellectual development is common, but disturbances in motor functions may not appear until later in life.

OCTOCEPHALY is a lethal condition in which the primary feature is agnathia—a developmental anomaly characterized by total or virtual absence of the lower jaw. The condition is considered lethal because of a poorly functioning airway.

In octocephaly, agnathia may occur alone or together with holoprosencephaly.

Another group of less common cephalic disorders are the *craniostenoses*. Craniostenoses are deformities of the skull caused by the premature fusion or joining together of the cranial sutures. Cranial sutures are fibrous joints that join the bones of the skull together. The nature of these deformities depends on which sutures are affected.

BRACHYCEPHALY occurs when the coronal suture fuses prematurely, causing a shortened front-to-back diameter of the skull. The coronal suture is the fibrous joint that unites the frontal bone with the two parietal bones of the skull. The parietal bones form the top and sides of the skull.

OXYCEPHALY is a term sometimes used to describe the premature closure of the coronal suture plus any other suture, or it may be used to describe the premature fusing of all sutures. Oxycephaly is the most severe of the craniostenoses.

PLAGIOCEPHALY results from the premature unilateral fusion (joining of one side) of the coronal or lambdoid sutures. The lambdoid suture unites the occipital bone with the parietal bones of the skull. Plagiocephaly is a condition characterized by an asymmetrical distortion (flattening of one side) of the skull. It is a common finding at birth and may be the result of brain malformation, a restrictive intrauterine environment, or torticollis (a spasm or tightening of neck muscles).

SCAPHOCEPHALY applies to premature fusion of the sagittal suture. The sagittal suture joins together the two parietal bones of the skull. Scaphocephaly is the most common of the craniostenoses and is characterized by a long, narrow head.

TRIGONOCEPHALY is the premature fusion of the metopic suture (part of the frontal suture which joins the two halves of the frontal bone of the skull) in which a V-shaped abnormality occurs at the front of the skull. It is characterized by the triangular prominence of the forehead and closely set eyes.

What research is being done?

Within the Federal Government, the National Institute of Neurological Disorders and Stroke (NINDS), one of the National Institutes of Health (NIH), has primary responsibility for conducting and supporting research on normal and abnormal brain and nervous system development, including congenital anomalies. The National Institute of Child Health and Human Development, the National Institute of Mental Health, the National Institute of Environmental Health Sciences, the National Institute of Alcohol Abuse and Alcoholism, and the National Institute on Drug Abuse also support research related to disorders of the developing nervous system. Gaining basic knowledge about how the nervous system develops and understanding the role of genetics in fetal

development are major goals of scientists studying congenital neurological disorders.

Scientists are rapidly learning how harmful insults at various stages of pregnancy can lead to developmental disorders. For example, a critical nutritional deficiency or exposure to an environmental insult during the first month of pregnancy (when the neural tube is formed) can produce neural tube defects such as anencephaly.

Scientists are also concentrating their efforts on understanding the complex processes responsible for normal early development of the brain and nervous system and how the disruption of any of these processes results in congenital anomalies such as cephalic disorders. Understanding how genes control brain cell migration, proliferation, differentiation, and death, and how radiation, drugs, toxins, infections, and other factors disrupt these processes will aid in preventing many congenital neurological disorders.

Currently, researchers are examining the mechanisms involved in *neurulation*—the process of forming the neural tube. These studies will improve our understanding of this process and give insight into how the process can go awry and cause devastating congenital disorders.

Investigators are also analyzing genes and gene products necessary for human brain development to achieve a better understanding of normal brain development in humans.

Where can I go for more information?

For more information about disorders of the developing nervous system, cephalic disorders, or birth defects in general, you may wish to contact:

National Organization for Rare Disorders (NORD)
P.O. Box 1968
(55 Kenosia Avenue)
Danbury, Connecticut 06813-1968
(203) 744-0100
(800) 999-6673
www.rarediseases.org

The Lissencephaly Network
716 Autumn Ridge Lane
Fort Wayne, Indiana 46804-6402
(219) 432-4310
www.lissencephaly.org

March of Dimes Birth Defects Foundation
1275 Mamaroneck Avenue
White Plains, New York 10605
(914) 428-7100
(888) MODIMES (663-4637)
www.marchofdimes.com

Birth Defect Research for Children
930 Woodcock Road, Suite 225
Orlando, Florida 32803
(407) 895-0802
www.birthdefects.org

For more information on research on the cephalic disorders, you may wish to contact the NINDS Brain Resources and Information Network at:

BRAIN
P.O. Box 5801
Bethesda, Maryland 20824
(301) 496-5751
(800) 352-9424
www.ninds.nih.gov

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