Professional Ultrasound Services
244 20th Avenue San Francisco, CA 94121-2203
www.jimbaun.com (415) 751-4090

Neural Tube Defects

The term “neural tube defects” refers to a group of malformations including anencephaly, cephaloceles, and spina bifida.

Spina Bifida

Synonyms
Spinal dysraphism, rachischisis, meningocele, and myelomeningocele.

Definition
Spina bifida can be defined as a midline defect of the vertebrae resulting in exposure of the contents of the neural canal. In the vast majority of cases, the defect is localized to the posterior arch (dorsal) of the vertebrae. In rare cases, the defect consists of a splitting of the vertebral body.

Incidence
Spina bifida is the most common malformation of the CNS. The incidence varies according to many factors, such as geographical area, ethnic differences, and seasonal. Typically, these anomalies are very common in the British Isles and uncommon in the eastern world. Spinal defects are more frequent in Caucasians than in Orientals or blacks. These differences seem to persist even after migration, suggesting a genetic rather than an environmental effect.

Etiology
Most congenital anomalies of the spinal cord result from defective closure of the neural tube during the fourth week of development. These neural tube defects (NTDs) affect the tissues overlying the spinal cord: meninges, vertebral arches, muscles, and skin. Anomalies involving the vertebral arches are referred to as spina bifida. This term denotes non-fusion of the embryonic halves of the vertebral arches, which is common to all types of spina bifida. Severe anomalies also involve the spinal cord and meninges. Spina bifida ranges from clinically significant types to minor anomalies that are unimportant.

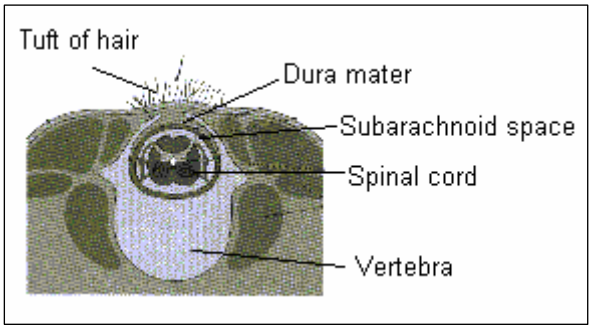
Nutritional and environmental factors undoubtedly play a role in the production of NTDs. Studies have shown that vitamins and folic acid supplements taken prior to conception reduce the incidence of NTDs (Van Allen et al., 1993; Forman

et al., 1995; Murphy et at., 1996). Certain drugs increase the risk of meningomyelocele (e.g., valproic acid). This anticonvulsant causes NTDs in 1 to 2% of pregnancies if given during early pregnancy (fourth week of development) when the neural folds are fusing. Pregnant animals exposed to hypothermia or high levels of vitamin A produce offspring with NTDs. Studies have also suggested that NTDs might result from specific biochemical abnormalities of the basement membrane, particularly hyaluronate, which plays a role in cell division and the shape of the primordial neuroepithelium

Pathology

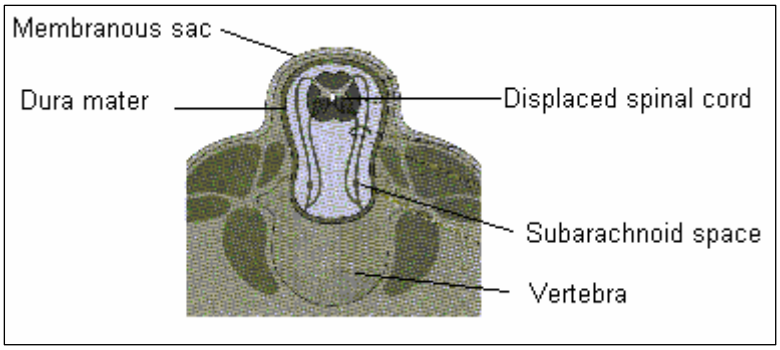
Spina bifida encompasses a broad spectrum of abnormalities. Lesions are commonly subdivided into ventral and dorsal defects. Ventral defects are extremely rare and are characterized by the splitting of the vertebral body and the occurrence of a cyst that is neuroenteric in origin. The lesion is generally seen in the lower cervical or upper thoracic vertebrae. Dorsal defects are by far the most common. They are subdivided into two types: *spina bifida occulta* and *spina bifida cystica (aperta)*.

Spina bifida occulta represents approximately 15 percent of the cases and is characterized by a small defect completely covered by skin. In many cases, this condition is completely asymptomatic and is diagnosed only incidentally at radiographic examination of the spine. In other instances, there is an area of hypertrichosis, pigmented or dimpled skin, or the presence of subcutaneous lipomas. A dermal sinus connecting the skin to the vertebrae and to the dura mater can occasionally be seen. The clinical importance of this lesion is its frequent association with infection of the neural contents.



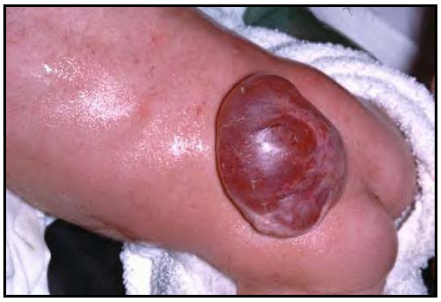
Spina bifida occulta

Spina bifida cystica (aperta): Severe types of spina bifida, involving protrusion of the spinal cord and/or meninges through the defect in the vertebral arches, are referred to collectively as *spina bifida cystica* because of the cyst-like sac that is associated with these anomalies. It is the most frequent lesion, resulting in 85 percent of dorsal defects and it occurs about once in every 1000



Spina bifida cystica

births. The neural canal may be exposed, or the defect may be covered by a thin meningeal membrane. More often, the lesion appears as a cystic tumor (spina bifida cystica). If the tumor contains purely meninges, the lesion is referred to as a "meningocele." More frequently, neural tissue is part of the mass, and the name meningomyelocele is used. If the spinal cord and/or nerve roots are included in the sac, the anomaly is called spina bifida with meningo-myelocele (Adjacent figure). Myelo refers to the spinal cord. Meningoceles are rare compared with meningomyelocele.



Meningomyelocele

Associated Anomalies

The two main categories of anomalies associated with spina bifida are other CNS defects and foot deformities. In almost all cases of *spina bifida cystica*, a typical abnormality of the posterior fossa is found. The lesion is Arnold-Chiari malformation type II (also called Chiari II malformation), and it is characterized by a herniation of the cerebellar vermis into the upper cervical spinal fossa through the foramen magnum. The fourth ventricle is displaced downward inside the neural canal and the posterior fossa appears shallow with the tentorium dis-placed downward. Displacement and kinking of the medulla are also observed. Chiari II malformation is almost invariably associated with obstructive hydrocephalus. The cause of the hydrocephalus is related to the low position and mechanical obstruction of the outflow from fourth ventricle, which normally drains the CSF into the spinal canal

Dislocation of the hip and foot deformities (clubfoot, rockerbottom foot) are frequently seen in association with spina bifida. The pathogenesis of the malformation is related to damage to nerve groups that enervate muscle groups to the lower extremities. Chronic contractures of the muscle groups in the foot result in clubfoot and rockerbottom foot in fetuses with spina bifida.

Prenatal Diagnosis

In recent years, specific biochemical screening programs have been developed to test for fetal anomalies. These tests are referred to as *multiple marker* screening, and include maternal serum alpha-fetoprotein (**MSAFP**), human chorionic gonadotropin (**hCG**), and estriol (**uE3**). Specifically, they increase the detection of open neural tube defects (ONTD's), Down's syndrome (Trisomy 21), and Edward's Syndrome (Trisomy 18).

Alpha-fetoprotein (AFP) is a protein produced primarily by the fetal liver. It seeps into the maternal blood and can be detected by radioimmuno-assay in routine blood test (MSAFP).

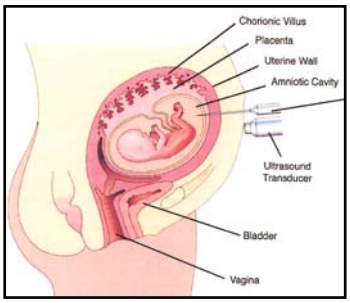
Elevated MSAFP (≥2 MOM) may be associated with:
- Wrong dates
- Multiple gestations
- Open neural tube defects
- Ventral wall defects
- Other fetal anomalies

Decreased MSAFP Is associated with:
- Trisomies 13, 18, 21
- Wrong dates
- Fetal demise

When the MSAFP level is not at expected levels, a ***Level II sonogram*** is performed to:
- Establish dates
- Rule out multiple gestations
- Identify fetal anatomic abnormalities

Human chorionic gonadotropin (hCG) and **unconjugated estriol** (uE3) are effective in screening for Down's syndrome (Trisomy 21). hCG tends to be elevated (2 times the median value) and uE3 tends to be lower than normal in Down's syndrome fetuses. In Edward's Syndrome (Trisomy 18), the maternal serum levels of AFP, hCG, and uE3 are all decreased.

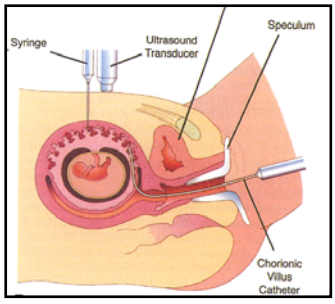
Amniocentesis



If a Level II sonogram fails to establish the cause of abnormal multiple markers, an amniocentesis is offered to evaluate amniotic fluid levels of AFP (AFAFP), acetylcholinesterase levels, and for fetal chromosomal karyotyping. If either the AFAFP or acetylcholinesterase is elevated, an occult neural tube defect is most likely.

Genetic amniocentesis is usually performed at around 16 weeks gestation, most routinely for women of "Advanced Maternal Age (AMA) who are over 35 years of age and for younger women who are at an increased risk for carrying a fetus with genetic abnormalities.

Chorionic Villus Sampling (CVS)



In an effort to provide genetic information about a fetus earlier in gestation, chorionic villus sampling was developed. Typically CVS is performed between 9 and 12 weeks gestation. The procedure can be performed either transcervically or transabdominally using direct ultrasound guidance. Trophoblastic cells that are

obtained with CVS can be cultured and karyotyped and in cases of chromosomal abnormalities, pregnancy can be terminated earlier.

Primary Sonographic Findings

The criteria for the diagnosis of spina bifida are based upon soft tissue and bony signs. The soft tissue signs include absence of skin covering the defect and presence of a bulging sac that may correspond to a meningocele or myelomeningocele. The bony signs are derived from the vertebral abnormalities associated with spina bifida. A clear understanding of the normal anatomy of the spine in different scanning planes is absolutely essential to the diagnosis.

It is a common belief that indirect signs of spina bifida, such as paralysis of the lower extremities and bladder distention, can be useful in the diagnosis of the lesion. The reader is alerted to the unreliability of such signs. We have seen apparently normal motion of the lower extremities in many fetuses with severe defects. The presence of a clubfoot, which is frequently associated with this defect, increases the index of suspicion in a patient at risk, as does the observation of hydrocephaly.

Secondary Sonographic Findings

Spina bifida is associated with a variety of typical intracranial abnormalities, including hydrocephalus (ventriculomegaly) and hypoplasia of the posterior fossa structures. As the fetal head is easily accessible to sonographic examination, identifying alterations of the cerebral architecture associated with or predictive of spina bifida assists in both targeted examinations of fetuses at risk for spina bifida and in screening sonograms at 18020 weeks in the general population.

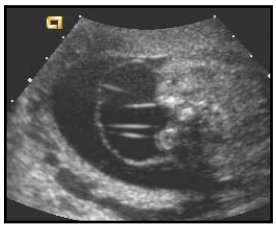
A typical abnormality of the cerebellum found in spina, which appears on sonography as a crescent with the convexity pointing posteriorly, is called the "*banana sign*". The usual "3" sign of fluid in the cisterna magna outlining the cerebellar hemispheres is obliterated by downward displacement of the medulla oblongata and lower cerebellum into the upper cervical column. The effaced cerebellar hemisphere assume a banana-like appearance.

Another abnormality of the cranium that may be found in cases of spina bifida is called the *"lemon sign.* Posterior and inferior displacement of the intracranial contents causes the frontal bones to deflect inferiorly resulting in a lemon-shaped cranium when viewed axially .

Summary of Sonographic Findings

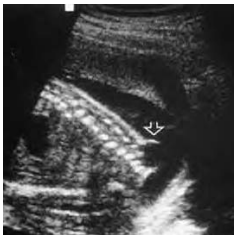
TRANSVERSE

- Splaying of posterior ossification centers into a "U" or "V" shape.
- When sac is intact, a cystic structure may be seen extending from the back. Appearances include: a small, simple cystic structure, a cyst with septations and/or solid matter.



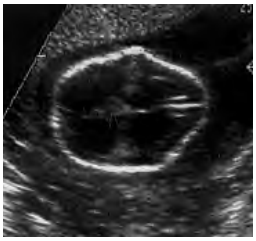
SAGITTAL

- Splaying of parallel lateral ossification centers.
- Associated with hydrocephalus, encephalocele and Arnold-Chiari II malformation.

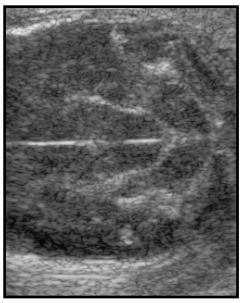


INTRACRANIAL

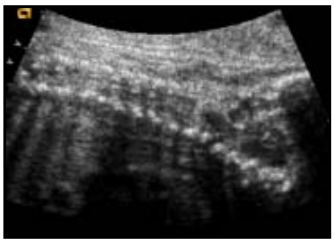
- LEMON SIGN: overlapping of the frontal bones creating a lemon shaped fetal head.



- BANANA SIGN: effacement of the cisterna magna due to downward displacement of the cerebellum



- ARNOLD-CHIARI Type II MALFORMATION: displacement of the lower cerebellum into the upper cervical column with dislocation of the medulla oblongata and 4th ventricle



Prognosis

Spina bifida is a serious congenital anomaly. The stillbirth rate is widely quoted to be 25 percent. The majority of untreated infants die within the first few months of life. Survival of infants treated in the early neonatal period is only 40 percent at 7 years. Twenty-five percent of these infants are totally paralyzed, 25 percent are almost totally paralyzed, 25 percent require intense rehabilitation, and only 25 percent have no significant lower limb dysfunction. Seventeen percent of infants at late follow-up have normal continence. At present, it is impossible to predict *in utero* the outcome of these infants. Prognostic factors include the level and extent of the lesion (cervical and high thoracic lesions are frequently fatal) and kyphoscoliosis . The presence of severe hydrocephaly has always been considered a poor prognostic sign. Early neonatal shunting has

significantly improved the intellectual development of these infants. Mapstone et al. reported that in a group of 75 infants with spina bifida, the mean IQ of those not requiring shunting procedures was 104, whereas those shunted in the absence of complications had a mean IQ of 91. The occurrence of complications, such as ventriculitis, lowers the mean IQ to 70.

All infants with spina bifida have some degree of Arnold-Chiari type II malformation. This condition is symptomatic (e.g., dyspnea, swallowing difficulties and a contracture disorder called opisthotonos) and represents a potentially fatal complication only in a small number of cases. Death is usually related to respiratory failure. In a series, 45 infants with symptomatic Arnold-Chiari malformation underwent laminectomy for relief of brain stem compression. The mortality rate was 38 percent in a follow-up period ranging from 6 months to 6 years.

Anencephaly

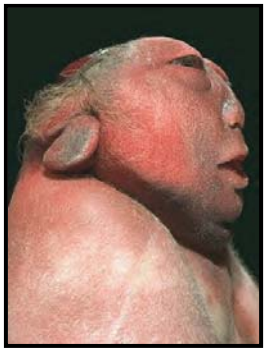
Synonyms
Pseudoencephaly, extracranial dysencephaly, acleidencephaly

Definition
Anencephaly is an anomaly characterized by the absence of cerebral hemispheres and cranial vault.

Incidence
The epidemiology of anencephaly is very similar to that of spina bifida. There is considerable variation in the prevalence of this condition in different parts of the world. In neonates, the anomaly is more frequent in females than in males. The incidence of anencephaly in abortion material has been found to be five times greater than that observed at birth.

Etiology
Anencephaly, as well as spina bifida, has a recognized multifactorial etiology. A number of teratogenic agents, including radiation, trypan blue, salicylates, sulfonamides, and CO_2 excess and anoxia, etc., have induced this anomaly in experimental animals.

Embryology
There are two main theories regarding the origin of anencephaly. The first proposes that the defect is due to failure of closure of the anterior neuropore and the second suggests that an excess of CSF causes disruption of the normally formed cerebral hemispheres.



Pathology
Most of the cranial vault is absent. The frontal bone is defective above the supraorbital region, and the parietal

bones, as well as the squamous portion of the occipital bone, are absent. The crown of the head is covered by a vascular membrane known as an angiomatous stroma. Beneath this membrane, few remnants of the cerebral hemispheres can be found. The diencephalic and mesencephalic structures are either completely or partially destroyed. The midbrain and hindbrain structures are generally preserved.

Other features that are quite characteristic of anencephalic infants include bulging eyes, a large tongue (macroglossia), and a very short neck.

Associated Malformations

Spina bifida is present in 17 percent of patients (craniorachischisis), cleft lip or palate in 2 percent, and clubfoot in 1.7 percent. Omphaloceles have also been described in some cases.

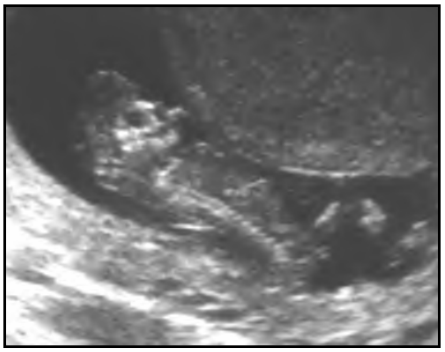
Diagnosis

Anencephaly was the first congenital anomaly identified in utero with ultrasound. The diagnosis relies on the failure to demonstrate the cranial vault. The anencephalic fetus has a typical froglike appearance and usually has a short neck. The diagnosis can probably be made as early as the 12th to the 13th week. In the third trimester, the diagnosis is quite obvious when the fetus is in transverse or breech presentation. However, difficulties can be encountered when a fetus is in vertex presentation because the base of the skull is often seen deep in the maternal pelvis, and there is only a perception that there is not enough room for a normal head in the lower uterine segment. The differential diagnosis between anencephaly and severe forms of microcephaly can be difficult.

Polyhydramnios is frequently associated with anencephaly. The mechanism is unclear, and several hypotheses have been suggested, including failure to swallow because of a brain stem lesion, excessive micturition, and failure of reabsorption of CSF. A frequent accompanying phenomenon is increased fetal activity. The explanation remains unknown, but irritation of the meninges and neural tissue by CSF has been proposed.

Anencephaly - Summary of Sonographic Findings:

- Fetal head should be identifiable by 12 weeks, definitively by 15 weeks at latest.
- Major portions of cranium and intracranial structures are absent. Orbits and face are usually present.
- Associated polyhydramnios (40-50%).



Encephalocele

Synonyms
Encephalocele, cranial or occipital meningocele, and cranium bifidum.

Definition
Cephalocele is a protrusion of the intracranial contents through a bony defect of the skull. The term “cranial meningocele” is used when only meninges are herniated. The term “encephalocele” defines the presence of brain tissue in the herniated sac. Encephalocele is commonly but incorrectly used to refer to both conditions.

Incidence
Rare. Occipital cephaloceles are by far the most frequent form in the Western world. In England, the frequency of this condition has been estimated to be 0.3 to 0.6 in 1000 births.

Etiology
Other neural tube defects are often found in siblings of infants with cephalocele, implying a familial tendency. Besides the conditions associated with neural tube defects, cephaloceles are frequent components of a number of genetic (e.g., Meckel syndrome) and nongenetic (e.g., amniotic band syndrome) syndromes. They have also been reported in association with maternal rubella, diabetes, and hyperthermia and can be produced experimentally in animals by the administration of several teratogens, such as x-ray radiation, trypan blue, and hypervitaminosis A.

Embryology
The basic disorder responsible for the defect is unknown. It has been suggested that overgrowth of the rostra! portion of the neural tube may interfere with the closure of the skull. Alternatively, the defect may result from failure of closure induction by the mesoderm. Most cephaloceles are, therefore, located in the midline. An exception to this occurs in cases of amniotic band syndrome, in which cephaloceles may be multiple, irregular, or asymmetrical.

Pathology
According to the bone in which the defect is located, cephaloceles are commonly subdivided into occipital, parietal, and frontal. By far the most common location is the occipital bone. The lesion may vary in size from a few millimeters to a mass larger than the cranial vault. It may contain only meninges (meningocele) or variable amounts of brain tissue (encephalocele). In some cases, most of the brain tissue is contained in the herniated sac. Frontal cephaloceles occur more frequently between the frontal and ethmoidal bones (frontonasal cephalocele).

Not all cephaloceles are externally evident. Some occur through a defect located in the base of the skull and protrude inside the orbits, nasopharynx, or

Associated Anomalies

As previously mentioned, cephaloceles can be found as part of a number of specific syndromes. In addition, both meningoceles and encephaloceles are associated with other CNS abnormalities. Hydrocephalus has been reported in 80 percent of occipital meningoceles, 65 percent of occipital encephaloceles, and 15 percent of frontal cephaloceles. Spina bifida is found in 7 to 15 percent of all cephaloceles.[1] Microcephaly was observed in 20 percent of cases studied. By definition, the herniation of the cerebellum inside the cephalocele is termed "Chiari type III deformity." This deformity, combined with aqueductal stenosis, is the major cause of hydrocephalus in these infants. Frontal cephaloceles are often associated with the median cleft face syndrome, characterized by hypertelorism and median cleft lip or palate.

Diagnosis

Traditionally, the diagnosis of cephalocele relies on the demonstration of a paracranial mass. However, this criterion is insufficient to distinguish them from other non-neural masses, such as cystic hygromas, and soft tissue masses, such as scalp edema. For this reason, an effort should be made to identify the skull defect.[1] This may be difficult, since the bony defect is usually smaller than the herniated mass and sometimes falls below the resolutive power of current ultrasound equipment. In axial scans, the complete contour of the occipital and frontal bones is not adequately visualized because of sound refraction. Furthermore, the normal sutures can be confused with a defect.

Hints for a proper differential diagnosis are: (1) cephaloceles are often associated with hydrocephaly, (2) brain tissue can be seen in some cephaloceles, (3) cystic hygromas usually have multiple septa, are often associated with other signs of hydrops, and have a paracervical origin, and (4) severe scalp edema can be confused with a cephalocele, but usually a sagittal scan can identify an intact skull and the diffuse nature of the condition.

Amniotic fluid alpha-fetoprotein (AFAFP) is usually elevated when the brain tissue or meninges are exposed. However, we have seen one case with a defect covered by skin in which the level of AFAFP was normal.

Whenever the diagnosis of a cephalocele is made, a careful examination of the fetus is indicated to search for other associated anomalies.

Encephalocele - Summary of Sonographic Findings

- Mass extending from calvarium. May be totally cystic, cystic with septations (meningocele), or may contain brain (encephalomeningo-myelocele).
- Cranial defect is occasionally seen.
- Cranial cavity appears small if a significant portion of brain is herniated.
- Associated with hydrocephalus, polyhydramnios

Prognosis
The prognosis of cephaloceles depends on three factors: (1) the presence of brain in the herniated sac, (2) hydrocephalus, and (3) microcephaly. The most important prognostic factor is the herniation of the brain. The mortality rate in these cases has been reported to be 44 percent versus no deaths observed in cases of simple meningocele.[1] Intellectual development was normal in only 9 percent of patients in the former group and 60 percent in the latter.

Iniencephaly

Definition
Iniencephaly is a complex developmental abnormality characterized by an exaggerated lordosis of the spine, usually associated with spina bifida and cephalocele.

Epidemiology
It is an extremely rare condition. The reported frequency has varied from 1:896 in England to 1:65,000 in India.

Etiology
Occurrence in siblings has been observed in only 1 patient of 57. Females are more frequently affected than males (M: F ratio = 0.28). Iniencephaly has been reported in association with maternal syphilis and with sedative intake. It can be produced in animals by the administration of vinblastine, streptonigrin, and triparanol.

Embryology
Different hypotheses have been postulated. Persistence of the embryonic cervical lordosis at the third week, leading to failure of closure of the neural tube, or abnormal development of the rostral portion of the notocord and somites of the cervicooccipital region are the most widely accepted theories.

Pathology
The criteria for the diagnosis of iniencephaly are (1) imperfect formation of the base of the skull, particularly at the level of the foramen magnum, (2) rachischisis, and (3) exaggerated lordosis of the spine. The spine is short and grossly abnormal, with kyphoscoliosis.

Associated Anomalies
Eighty-four percent of iniencephalic infants have other associated anomalies, including anencephaly, cephaloceles, hydrocephaly, cyclopia, absence of mandible, cleft lip and palate, cardiovascular anomalies, diaphragmatic hernia, single umbilical artery omphalocele, gastroschisis, situs inversus, polycystic kidneys, arthrogryposis, and clubfoot.

Diagnosis

The two diagnostic clues are extreme dorsal flexion of the head and an abnormally short and deformed spine. The differential diagnosis includes anencephaly, the Klippel-Feil syndrome (shortness of the neck associated with fusion of cervical vertebrae), and a cervical myelomeningocele. Anencephaly can be identified by an absent calvarium. The differential diagnosis with Klippel-Feil syndrome appears to be difficult. As a matter of fact, some authors consider the Klippel-Feil syndrome and iniencephaly as different abnormalities of the same spectrum. However, in the former, gross and devastating abnormalities of the spine are absent. The presence of a cervical myelomeningocele raises the index of suspicion.

Iniencephaly - Summary of Sonographic Findings

- Exaggerated, hyperextension of the fetal head
- Demonstration of cervical spina bifida

Prognosis

This entity is virtually always fatal in the neonatal period. Three long-term survivors have been reported. However, the iniencephalic deformity was very mild in these infants, and it is doubtful that they would have been identified in utero by ultrasound.