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Ultrasound Diagnosis of Congenital Brain Anomalies

Brankica Vasiljevic[1], Miroslava Gojnic[1] and Svjetlana Maglajlic-Djukic[2]
[1]*Institute of Gynecology and Obstetrics – Clinical Centre of Serbia,*
[2]*University Children´s Hospital,*
Belgrade,
Serbia

1. Introduction

Congenital malformations affect approximately 2-3% of all live births every year (Whiteman et al, 1994; Atlas *et al*, 1985). Congenital brain anomalies, whether they are isolated (single) or part of syndromes, are a common cause of medical intervention, long-term illness, and death. The neonatologist or perinatologist often is the first person to identify necessary evaluations and management and to explain the cause of the anomalies and the prognosis for the child to the parents. Different anomalies may be classified as malformations, deformations and disruptions (Smith & Smith 2006; Barkovich *et al* 2001, Barkovich, 2005). Co-existent group of anomalies is described as polytopic field defect, sequence, syndrome and association. Other classification may be major and minor anomalies. Major anomaly is one with a medical, surgical or cosmetic importance and with impact on morbidity and mortality. Minor anomaly is one that does not have a serious surgical, medical or cosmetic significance and does not affect normal life expectancy or lifestyle.

Central nervous system (CNS) anomalies are the second most frequent serious congenital anomaly, after congenital heart disease. There is significant variation in incidences of congenital CNS anomalies in different regions of world including Europe (Barkovich, 2005). Congenital CNS anomalies are a heterogeneous disease for which genetic, infectious, teratogenic and neoplastic causes have been implicated (Bendon, 1987; Barkovich *et al*, 2005). Table 1. show the frequency of different CNS congenital anomalies which were detected in our institute during fourth years study period.

The development of the brain and spinal cord is an extremely complicated process which continues into second decade before final maturity is achieved. Abnormality in the development of CNS are common, up to 75 % of fetal deaths and 40% of deaths in infancy are due to CNS malformations (Barkovich, 2005). Furthermore, one third of all congenital abnormalities identified in the perinatal period arise from the central nervous system. These abnormalities are often evident at birth, but some cerebral malformations may not be immediately obvious. The neonates with dysmorphic feature or abnormal neurological behaviour may suggest cerebral malformations, and various imaging techniques are essential for further clarification. Due to the wide spectrum of congenital CNS

abnormalities, only the more common ones amenable will be discussed here. Ultrasound (US) examination is an effective modality for the diagnosis of these anomalies in experienced hands. Cranial US correlate well with anatomical and pathological findings and clinical outcomes. Cranial US detection of congenital brain anomalies is useful for diagnostic purposes, and it also may allow for more appropriate management and more accurate neurological prognostication.

Congenital CNS anomalies	2005	2006	2007	2008	∑	Incidence
ACC	1			1	2	0.07 : 1000
Arachnoid cysts			1		1	0.03 : 1000
CSD	3	3	8	11	25	0.9 : 1000
DWM			1	1	2	0.07 : 1000
Encephaloceles		1			1	0.03 : 1000
Spinal lipoma			1		1	0.03 : 1000
Holoprosencephaly	2		1		3	0.1 : 1000
Hydrocephalus	9	2	1	4	15	0.5 : 1000
MCM				1	1	0.03 : 1000
Myelomeningoceles	4	1	5	2	12	0.4 : 1000
Microcephaly	1	1		1	3	0.1 : 1000
Schizencephaly				1	1	0.03 : 1000
VGA		1			1	0.03 : 1000
Ventriculomegaly	12	8	7	13	40	1.3 : 1000
Births	7091	7070	7015	7012	28818	3.6 : 1000

Table 1. The frequency of different CNS congenital anomalies (ACC- Agenesis of the corpus callosum; CSD- Closed spinal dysraphisms; DWM- Dandy-Walker malformation; MCM- Mega cistern magna; VGA-Vein of Galen aneurysm).

2. Cranial ultrasonography

In the neonatal period cranial US can be used as the initial modality to exclude a major structural malformation (Fawer, 1985; Carty *et al*, 2001, Barkovich, 2005; Von Wezel-Meijler G, 2007). Cranial ultrasonography (US) was introduced into neonatology in the late 1970s and has become an essential diagnostic tool in modern neonatology. It is non-invasive highly sensitive, safe, easily repeatable, accurate and cost effective neuroimaging technique. The advantages of cranial US are that it can be performed at the bedside with minimal disturbance to the neonates and patients do not require sedation. It is a useful modality for detecting congenital and acquired anomalies of the brain and the most frequently occurring patterns of brain injury in both preterm and full-term neonates. Cranial US is also suitable for assessing brain maturation and timing of cerebral injury. It can be initiated at a very early stage, even immediately after birth. Cranial US is relatively inexpensive compared with other neuro-imaging techniques. The non-invasive nature of cranial US make it an ideal imaging technique in the neonate. During the late foetal and perinatal period and during early infancy, major maturational processes and growth of the brain take place

(Barkovich *et al*, 2001; Carty *et al* 2001). Maturational processes include a major increase in volume, weight, and surface area of the brain; gyration; cell migration; germinal matrix involution; and myelination. These maturation processes can be visualised by modern neuro-imaging techniques. Gyration is a phenomenon occurring late during fetal development and can be observed by the second month of intrauterine life. It goes on to the end of the pregnancy and even later after birth. The primary sulci appear as shallow grooves on the surface of the brain that become progressively more deeply infolded and that develop side branches, designated secondary sulci. Gyration proceeds with the formation of other side branches of the secondary sulci, referred to as tertiary sulci. The timing of the appearance of these different types of sulci is so precise that neuropathologists consider gyration to be a reliable estimate of gestational age and consequently a good marker of fetal brain maturation (Figure 1.).

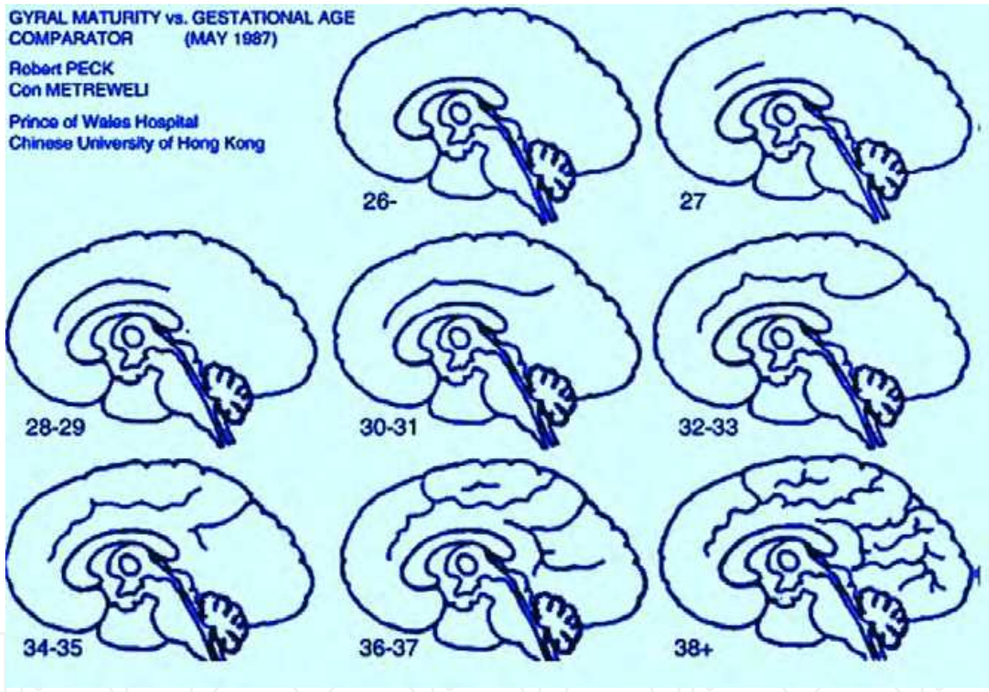
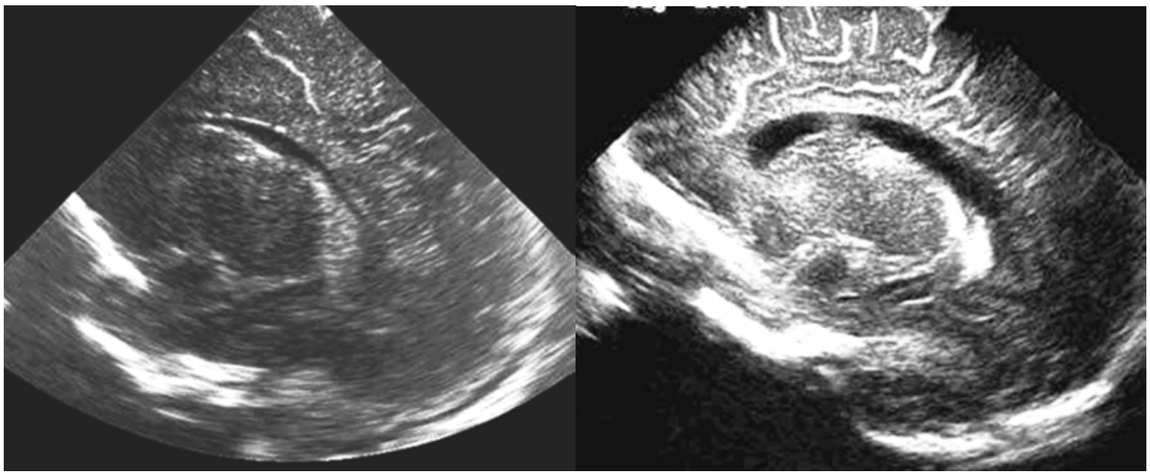


Fig. 1. Comparative sagittal sections show a gyral pattern from 26-38+ weeks of gestation.

It is possible to assess the gestation age of the infant from the ultrasound images (Figure.2.). In extremely preterm infants (gestation age from 24–26 weeks), the brain surface is still very smooth and has a lissencephalic appearance. The process of gyration can be followed by cranial US and cortical sulcation is considered to be a good marker of neonatal brain maturation by neuropathologists (Barkovich, 2005; Von Wezel-Meijler, 2007). Familiarity with the normal ultrasonographic imaging appearances of the fetal/neonatal cerebral cortex at various stages of gestation is essential for the early detection of abnormal sulcal development. Abnormal cortical development is the main manifestation of lissencephaly, although other associated CNS anomalies (e.g. ventriculomegaly, holoprosencephaly, agenesis of the corpus callosum, porencephaly, encephalocele).

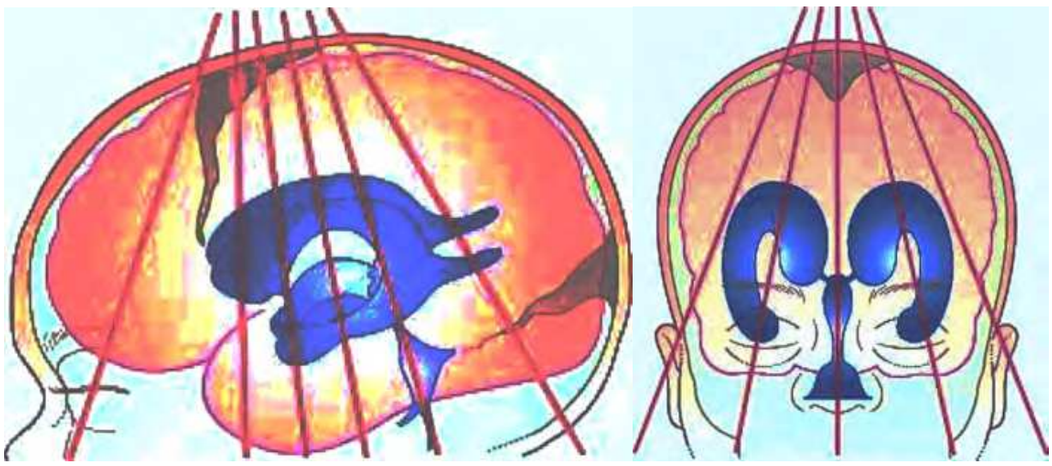


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Fig. 2. Comparative US sagittal sections show a gyral pattern in neonate with 27 weeks of gestation (A) and 38 weeks of gestation (B).

The germinal matrix is an abundant, highly cellular and vascular "strip" of subependymal tissue. During early gestation it lines the entire wall of the lateral ventricles and third ventricle. It produces neuroblasts and glioblasts and is the origin of migrating neurons (first trimester) and glial cells (second and third trimesters). Regression of the germinal matrix starts from 24–26 weeks of gestation onwards. After 34 weeks, remnants remain in the thalamo-caudate notch and temporal horns of the lateral ventricles. In the foetus and very preterm infant, the lateral ventricles are often wide and asymmetric (usually the left is larger than the right) with very wide occipital horns. Subarachnoid spaces may also be wide. The cerebral lateral ventricles have a complex threedimensional architecture that undergoes major developmental changes throughout gestation. Normal sizes of ventricles provide reassurance of the normal development of the neonatal brain. Lateral ventricles are slightly, but significantly, larger in male than in female fetuses. Therefore, it is not surprising that males are found to have borderline ventriculomegaly more frequently, and to have a significantly lesser degree of neurological compromise than females (Pilu *et al*, 1999). Spontaneous remission of borderline ventriculomegaly is frequently documented. It is unclear whether or not this implies an amelioration of the prognosis. Some investigators failed to demonstrate a difference in the outcome between cases with stable or progressing ventriculomegaly and cases with spontaneous remission (Pilu *et al*, 1999). Mild ventriculomegaly may be the first sign of abnormal or delayed brain maturation. It is possible that isolated borderline ventriculomegaly may represent the earliest manifestation of brain damage from heterogeneous causes including primary cerebral maldevelopment (e.g. obstructive hydrocephalus, lissencephaly) and destructive lesions (e.g. periventricular leukomalacia) arising from hypoxia and/or infections. Gross enlargement consistently indicates major cerebral anomalies.

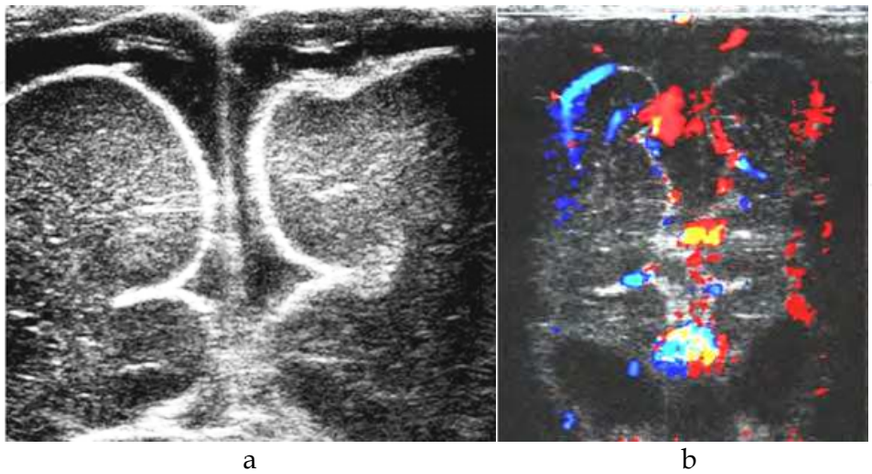
Standard cranial US scanning is performed through the anterior fontanel, the whole brain is scanned, and images are recorded in at least six coronal and five sagittal planes with a high frequency sector transducer (7.5-10 MHz). These imaging planes are shown in Figure 3.



a b

Fig. 3. Technique of intracranial scanning: (A) coronal planes; (B) sagittal planes.

An additional scan series can be obtained in the axial plane through the temporoparietal bone. The standard coronal and sagittal views are used to assess the symmetry of the cerebral hemispheres, absence of the CSP and the corpus callosum, morphology of the cerebral ventricles, thalami and the posterior cranial fossa structures (e.g. cerebellum, the cisterna magna and the fourth ventricle). A high frequency linear transducer (10 MHz) is very useful to examine the subarachnoid and subdural space and integrity of the spine (Figure 4.a.). Doppler is extremely useful for the routine cranial examination. This is particularly true when trying to differentiate subdural from subarachnoid fluid in the subarachnoid spaces (Figure 4.b.) and in any suspected vascular lesion such as a vein of Galen anomaly (Chavhan *et al*, 2008). Cranial US are correlated with anatomical and pathological findings and clinical outcomes. Appropriate correlation of the US features with clinical history can assist in improving the diagnostic yield. Familiarity with the US features of congenital brain anomalies is therefore an extremely valuable tool, as it facilitates an accurate diagnosis and treatment these anomalies.

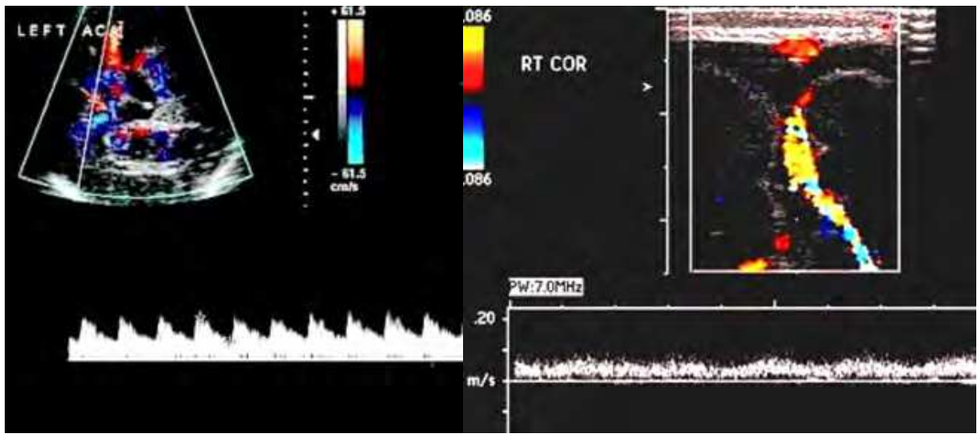


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Fig. 4. Normal surface subdural and subarachnoid spaces in coronal view using a high frequency linear transducer (A) and color Doppler (B).

2.1 Color doppler ultrasound

The use of pulsed and continuous color Doppler US allows simultaneous examination of parenchymal and vascular cerebral structures (Cheung *et al*, 1994; Vasiljevic *et al,* 2011). Pulsed and continuous color Doppler neuroimaging are used to assess cerebral blood flow in many pathological states including hypoxic ischemic change and congenital abnormalities. Doppler flow measurements may help to distinguish between vascular structures and non-vascular lesions. Cerebral blood flow accounts for 22%–25% of the cardiac output in neonates and 15% of that in adults (Couture, 2001). Every major vessel in the human body has a characteristic flow pattern that is visible in spectral waveforms obtained in that vessel with Doppler US. Familiarity with the Doppler waveforms characteristic of cerebral arteries and veins in neonates is important for accurate diagnosis of brain abnormalities (Figure 5.).



a b

Fig. 5. Normal color Doppler wave forms from the anterior cerebral artery (A) and the superior sagittal sinus (B).

The wave forms may be affected by age- and development-related hemodynamic differences (Chavhan *et al,* 2008, Romagnol *et al,* 2006). Values of cerebral blood flow velocities progressive increase with gestation age on consequence of progressive increase cardiac output, blood pressure and closing ductus arterosus (Vasiljevic *et al,* 2010). Values of Doppler indices (Pourcelot index or the resistance index and Gossling index or the pulsatility index) gradually increase with gestation age in consequence of progressive maturation and opening of vascular cerebral bed with a reduction of the cerebrovascular resistance (Vasiljevic *et al,* 2008; Deeg & Rupprecht, 1988). In the first 2 or 3 months after birth, complex variations in cerebral hemodynamics occur in association with changes in pO_2, pCO_2, and ductus arteriosus closure. Vasodilatation is seen with hypoxemia and hypercapnea. After the 3rd day of life, there is a gradual increase in peak systolic velocity and end-diastolic velocity. All cerebral arteries display a low-resistance flow pattern with continuous forward flow during systole and diastole (Figure 5.a.). Because these arteries usually have a diameter of less than 5 mm, the spectral lines are broad and the spectral window is filled. Knowledge of normal values of cerebral blood flow velocities and Doppler indices in neonates different gestation age is important for the monitoring maturational processes and growth of the immature brain and also useful for differential diagnosis of congenital and acquired CNS anomalies in both preterm and full-term neonates (Chavhan *et*

al, 2008;). Normal neonatal values and postnatal changes of cerebral blood flow velocities have been reported by several examiners (Deeg & Rupprecht 1989; Romagnol *et al,* 2006; Vasiljevic *et al*, 2010). Table 2. shows the normal values of cerebral blood flow velocities and 3 Doppler indices in the anterior cerebral artery in neonates different gestation age. These values we have obtained with color Doppler technique in seventy healthy neonates different gestation age during two years study period.

Neonates	GA	BW (g)	PSV (cm/s)	EDV (cm/s)	RI	PI
10	27.3±0.5	950±110	21.30 ±0.45	6.40±0.20	0.59±0.10	1.06±0.08
20	29.5±1.2	1350±170	24.20 ±0.65	7.00±0.30	0.60±0.10	1.10±0.15
20	34.5±0.6	1950±340	27.00 ±0.75	7.80±0.50	0.63±0.08	1.15±0.30
20	38.6±1.3	3540±640	32.50 ±0.90	9.95±0.40	0.65±0.05	1.18±0.35
Σ 70	34.5± 5.5	2540 ±950	26.25±0.68	7.78±0.35	0.61±0.08	1.12±0.22

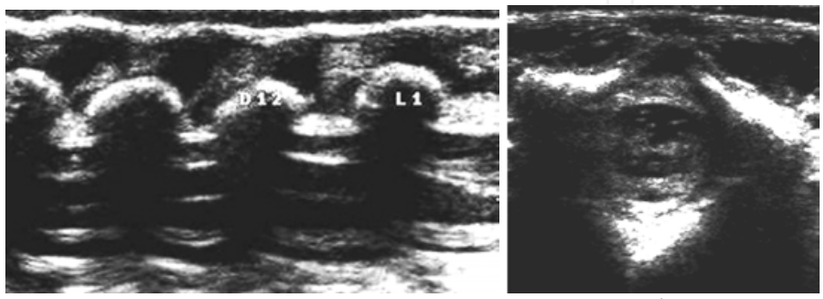
Table 2. Normal values of cerebral blood low velocities in the neonates in the neonates (GA-gestational age; PSV- peak-systolic velocity; EDV- end-diastolic velocity; RI- resistive index and PI- pulsatility index).

Referred cardiac pulsations normally can be seen in the intracranial veins. Venous waveforms in the superior sagittal sinus may be continuous and monophasic or may fluctuate in synchronicity with arterial pulsations (Figure 5.b.). Intracranial venous flow velocities gradually increase after birth (Dean & Taylor, 1995). The mean velocity in the superior sagittal sinus usually ranges between 8 and 12 cm/s in neonates. The transverse sinus usually can be assessed in neonates and shows an intracranial venous flow velocity of 2.7–3.3 cm/s. However, great variations can be seen in flow velocity with factors such as head rotation, crying, and other activities. Cardiac output fluctuates in an unstable neonate, altering carotid artery and cerebral perfusion. Color Doppler imaging is also useful in defining the limit of the arterial system within the subarachnoid space. This helps differentiate fluid in the subdural space from adhesions within the arachnoid space, as the arterial system is confined to the subarachnoid space (Chavhan *et al,* 2008; Dean & Taylor, 1995)

2.2 Ultrasnography of the spine

Ultrasound does not penetrate through bone but in the neonate the posterior spinal arches are poorly mineralized, allowing US assessment of the cord and dural sac from the foramen magnum down to the sacral hiatus. Spinal US is used as an initial screening tool in the neonate with spinal and other congenital abnormalities. There is a high incidence of spinal abnormalities in babies who have other congenital syndromes (e.g., ano-rectal malformation, cloacal exstrophy, caudal regression and spinal segmentation abnormalities—the VATER/VACTEROL anomaly) (Pilu & Hobbins, 2002). Two types of scanning planes can be used to evaluate the integrity of the spine. In transverse planes or axial planes, the examination of the spine is a dynamic process performed by sweeping the transducer along the entire length of the spine and at the same time keeping in the axial plane of the level being examined. In transverse sections, the neural canal appears as a closed circle. It is lined anteriorly by the ossification center in the body of the vertebrae and posteriorly by the two ossification centers of the laminae (Figure 6.). The vertebrae have different anatomic configurations at different levels. Thoracic and lumbar vertebrae have a triangular shape, while the first cervical

vertebrae are quadrangular in shape, and sacral vertebrae are flat. In the longitudinal or saggital section, the spine appears as three parallel lines converging caudally in the sacrum. The lines correspond to the anterior and posterior walls of the spinal cord and a central echogenic line the central canal (Figure 6.). Spinal cord appears hypo-echoic. The cord is surrounded by the cerebrospinal fluid (CSF) which appears anechoic. In term neonates the conus medullaris is usually found at the level of L2-L3. If a true longitudinal section can be obtained, visualizing the conus medullaris in its normal location further strengthens the diagnosis of normalcy (Robbin *et al*, 1994). The filum terminale extends to the sacral region as a thin extension of the cord. The normal filum terminale is 1.0-1.5 mm in diameter. Filing the cord in this area are echogenic lines, nerve fibres, which almost fill the arachnoid space and can be seen to move on real-time imagining and form cauda eqina.



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Fig. 6. The longitudinal section of the neonatal spine (A) and the transverse views of the neonatal spine (B).

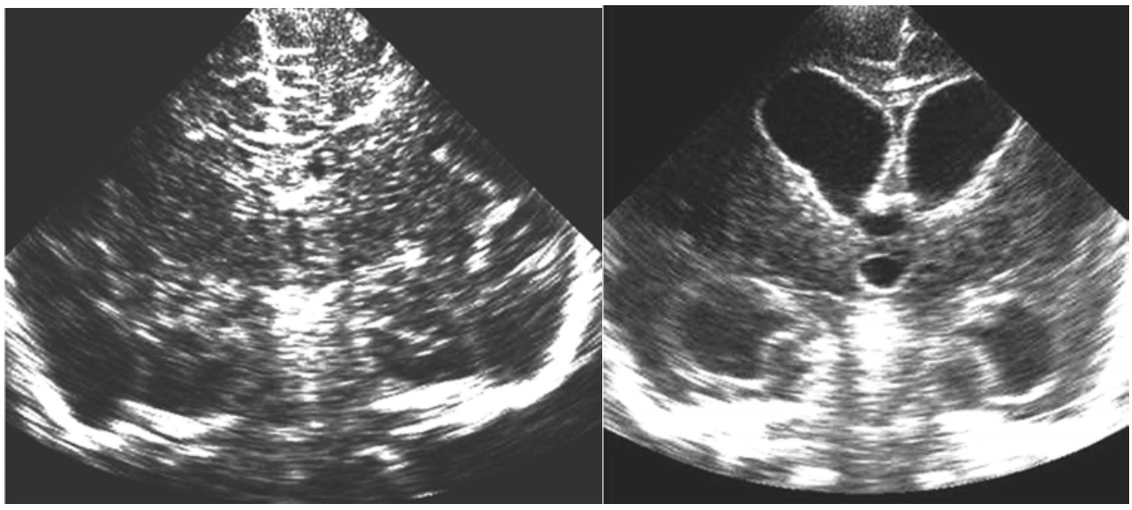
More recently three-dimensional ultrasound has become available. Three-dimensional ultrasound may facilitate the examination of the fetal brain and spine.

Its utility in the neonatal nursery needs further assessment, but it may be useful in assessing ventricular volumes and producing more meaningful images of cerebral abnormalities and brain damage (Riccabona *et al*, 2003). The main indication for MRI of the neonatal brain is further evaluation of inconclusive ultrasound findings in neonates with dysmorphic feature or abnormal neurological behavior.

3. Cerebral ventriculomegaly and hydrocephaly

Hydrocephalus and ventriculomegaly are both terms used to describe dilatation of the lateral ventricles. However, they should be distinguished: hydrocephalus signifies dilated lateral ventricles resulting from an increased amount of CSF inside the ventricles and increased intracranial pressure, while ventriculomegaly is a dilatation of the lateral ventricles without increased intracranial, from any cause, nonobstructive or obstructive. Ventriculomegaly is the most common congenital CNS anomaly with an incidence of 0.3 to 1.5 per 1000 births, probably higher in utero (Fransen *et al*, 1996). Couples with a previously affected child have a recurrence risk of 4% (Griffiths *et al,* 2006). Ventriculomegaly can be isolated or associated with other congenital (e.g. Dandy Walker malformation, corpus callosum agenesis, arachnoid cysts, vein of Galen aneurysms and a spinal defect with myelomeningocele) or acquired CNS anomalies (hemorrhage, infections). Extra-cranial abnormalities occur in 30% of cases and included meningomyelocele, renal anomalies (e.g. bilateral or unilateral renal agenesis, dysplastic kidneys), cardiac anomalies (e.g. ventricular

septal defect, tetralogy of Fallot), gastrointestinal anomalies (e.g. colon and anal agenesis, malrotation of the bowel), cleft lip and palate, Meckel syndrome, gonadal dysgenesis, arthrogryposis, and dysplastic phalanges. Chromosomal aberrations are found in 11% of cases, mostly trisomy 21 (Schwanitz *et al,* 1993; Gaglioti *et al*, 2005). Isolated congenital ventriculomegaly accounts for 30-60% of neonates with enlarged lateral cerebral ventricles (Mercier *et al,* 2001). In the majority of cases, isolated ventriculomegaly is the consequence of an obstruction along the normal pathway of CSF (e.g. obstructive ventriculomegaly). Nonobstructive causes of ventriculomegaly include a congenital CNS malformation (failure of development of portions of the normal brain), brain destruction (e.g. congenital infection or a vascular mechanism) and overproduction of CSF (choroid plexus papillomas). Congenital ventriculomegaly is a heterogeneous disease for which genetic, infectious, teratogenic and neoplastic causes have been implicated. A multifactorial pattern of inheritance is probably responsible for most cases of congenital ventriculomegaly (Renier *et al,* 1988). X-linked hydrocephalus comprises approximately 5% of all cases. This condition is caused by mutations in the gene at Xq28 encoding for L1, a neural cell adhesion molecule. Mutations in this gene are also responsible for other syndromes with clinical overlap that are frequently referred to as the X-linked hydrocephalus spectrum and include MASA (e.g. mental retardation, aphasia, shuffling gait, adducted thumbs) syndrome, X-linked mental retardation-clasped thumb (MR-CT) syndrome, X-linked complicated spastic paraparesis (SP1), and some forms of X-linked agenesis of the corpus callosum (Kenwick *et al,* 1996). The presence of uni- or bilateral ventriculomegaly seems to be of some discriminatory value. Ventriculomegaly tends to be unilateral in cases of brain destruction and bilateral in cases of CNS malformation, and this difference is statistically significant. In apparently isolated ventriculomegaly, we must distinguish between borderline and moderate to severe ventriculomegaly (Graham *et al,* 2001; Toma & Granata, 2005). US is an effective mode for imaging the ventricular system and sensitive to ventricular dilatation and minor degrees of ventricular asymmetry (Kenwick *et al,* 1996). In the clinically normal term infant the ventricles are often small (slit-like) for the few days after vaginal delivery. The normal ventricular system, which appears as anechogenic fluid-filled space becomes dilated and increase in size (Figure 7.).



a b

Fig. 7. Normal ventricular system (A) and ventricular dilatation (B) in coronal view.

The most useful qualitative US features of early ventricular dilatation are ballooning of the supratentorial angles of the ventricles of the frontal horns in coronal plane. These areas dilate more than the trigones and bodies of the ventricles because they are lager and require less pressure for distension (Carty *et al*, 2001). Despite that, ventricular dilatation is usually first seen in the occipital horns of the lateral ventricles, but there is considerable variation in the size of this part of the ventricular system in normal babies. With modern real-time ultrasound, clear visualisation of the lateral ventricles can be obtained and exact anatomical landmarks identified. Lateral ventricular size has been measured with number of different methods. Levine et al measured the ventricular size from midline to the lateral-most point of the lateral ventricles (ventricular index) in 273 infant from 26 to 42week's gestation and described normal ranges of ventricular size at differing gestation (Levine *et al*, 1985). In addition, London et al measured the biventricular diameter at the level of the frontal horns, diagonal width of the frontal horns at level of the caudate nucleus, intercaudate distance and biventricular diameter at the body of the lateral ventricles (London *et al,* 1980). Allan et al and Qusling et al measured of the lateral ventricules at the mid-body near the atrium of ventricule in sagittal plane (Qusling yet al, 1983). This is regarded as a "standard table" for assessment of ventricular dilatation. The term borderline ventriculomegaly is commonly used to indicate cases characterized by an atrial width of 10–15 mm. Some authors have reported a different rate of abnormal neurologic outcome in fetuses with atria > 12 mm compared with those with atria measuring 10–12 mm (a mild form of borderline ventriculomegaly). In fact, an isolated borderline ventriculomegaly of 10–12 mm might be considered as a variant of the norm (Signorelli et al, 2004). When the atrial width is between 15–20 mm the ventriculomegaly is defined moderate. Aqueductal stenosis, regardless of its cause, is responsible for the progression of ventricular dilatation. Severe ventriculomegaly is usually referred to as hydrocephalus and is defined on the basis of an atrial width of more than 20 mm (Bloom *et al,* 1997) (Figure 7.b.). Congenital hydrocephalus is classified into three categories by causes that disturb the CSF circulation pathway: simple hydrocephalus, dysgenetic hydrocephalus, and secondary hydrocephalus. Simple hydrocephalus is caused by a developmental abnormality localized within the CSF circulation pathway and includes aqueductal stenosis, atresia of the foramen of Monro, Magendie or Luschka, and maldevelopment of arachnoid granulation. Dysgenetic hydrocephalus results from a cerebral developmental disorder in the early stages of development, and includes hydranencephaly, holoprosencephaly, porencephaly, schizencephaly, Dandy–Walker malformation, dysraphism, and Chiari malformation. Secondary hydrocephalus is a generic term indicating hydrocephalus caused by an intracranial pathologic condition, such as intracranial infection, hemorrhage or brain tumor.

Pediatric data suggest that a correlation exists between cortical mantle thickness before shunting and long-term intellectual performances. Thickness of less than 1 cm has been associated with a poor outcome, but the most important prognostic consideration is the presence and nature of the associated anomalies. The available evidence suggests that borderline ventriculomegaly is most frequently without consequences (Bloom *et al,* 1997). Some authors have opposite results, and suggest that borderline ventriculomegaly carries an increased risk of cerebral maldevelopment, delayed neurologic development, and possibly chromosomal aberrations (Pilu Falco *et al*, 1999; Mercier *et al,* 2001). The main problem in these cases with borderline ventriculomegaly is to exclude other CNS and extra-cranial malformations. Macrocrania at birth, ventricular size and age at surgery had no influence on the outcome. Ventriculomegaly may develop in late gestation or after birth, particularly with the X-linked hydrocephalus spectrum.

4. Agenesis of the corpus callosum

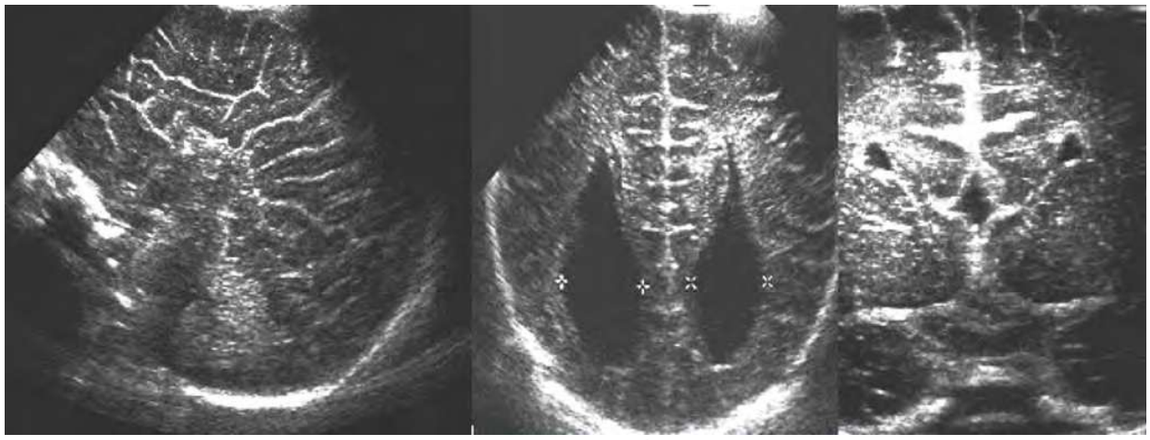
Agenesis of the corpus callosum is an anomaly that may occur in isolation or in association with other CNS or systemic malformations. Because the corpus callosum may be partially or completely absent, the term dysgenesis has also been used to describe the spectrum of callosal anomalies (Barkovich & Norman, 1988; Davila-Gutierrez, 2002). With complete agenesis, the corpus callosum is totally absent. With partial agenesis (hypoplasia), the anterior portion (posterior genu and anterior body) is formed, but the posterior portion (posterior body and splenium) is not. An atypical appearance occurs when the anterior to posterior formation is not respected (Barkovich, 1990). Development the corpus callosum occurs at the same time as cerebral and cerebellar development, and therefore agenesis of the corpus callosum is associated with other brain anomalies in 80% of cases. Associated CNS anomalies may include midline intracerebral lipomas, encephalocele, interhemispheric arachnoid cyst, microcephaly, Dandy-Walker malformation, Arnold-Chiari malformation, holoprosencephaly, hydrocephalus, disorders of neuronal migration, such as neuronal heterotopias, lissencephaly, pachygyria, and schizencephaly (Hetts *et al*, 2006; Volpe, 2009). With partial agenesis (hypogenesis), the anterior portion (posterior genu and anterior body) is formed, but the posterior portion (posterior body and splenium) is not. The rostrum and the anterior/inferior genu are also not formed. Secondary destruction of the corpus callosum occurs when the genu and anterior body are destroyed, leaving the posterior portion of the corpus callosum intact. Primary dysgenesis/agenesis of the corpus callosum should be differentiated from secondary destruction of an initially normally developed corpus callosum as can be observed in trauma, infarction, hemorrhage and in several metabolic diseases. Agenesis of the corpus callosum can occur in chromosomal abnormalities, such as trisomy 8, trisomy 13 and trisomy 18, as a part of the holoprosencephalic sequence, and also may be found in chromosomal translocation syndromes (Tang *et al,* 2009). Callosal anomalies are found in several syndromes, including X-linked Aicardi syndrome, the median cleft face syndrome, Andermann syndrome, F.G. syndrome, and acrocallosal syndrome. An association with maternal rubella and toxoplasmosis has been reported. Because they develop embryonically in close proximity, agenesis of the corpus callosum is commonly associated with malformations of local limbic structures, particularly the septum and hippocampal formations. Extra-CNS malformations may include anomalies of the face, musculoskeletal system, gastrointestinal tract, genitourinary tract, cardiovascular system, and respiratory system.

The incidence of agenesis of the corpus callosum is from 0.3–0.7% in the general population to 2–3% in the developmentally disabled population. Dependent on etiology, a recurrence risk is from 1% (if sporadic or chromosomal) to 25% (if autosomal recessive) or even 50% in males (if X-linked recessive).

The corpus callosum is a white matter structure connecting the cerebral hemispheres and is important in coordinating information and bilateral exchange of sensory stimuli. It develops between the 10th and 20th weeks of gestation, from the lamina reuniens, which is the thickened dorsal aspect of the lamina terminalis (Bennet *et al,* 1996). If the commissural plate fails to develop or is damaged, the uncrossed callosal fibers run parallel to the medial walls of the lateral ventricles, forming the bundles of Probst. These bundles do not cross the midline. Pathogenesis agenesis of the corpus callosum is uncertain, but callosal dysgenesis may be associated with a migration disorder (Smith *et al,* 2008). When complete, corpus

callosum consist of genu, body, splenum and rostrum. The normal development sequence is anterior to posterior, which allows one to distinguish between a partial primary and secondary dysgenesis of the corpus callosum. The genu is the first area to develop. Antenatal diagnosis of agenesis of the corpus callosum is possible from about 20 weeks' gestation.

The characteristic findings agenesis of the corpus callosum on ultasonography included absent corpus callosum and cavum pellucidum in coronal and saggital planes, widely separated lateral venticles, colpocephaly or "teardrop" configuration of lateral ventricles, elevation and variable dilatation of the third ventricle ("interhemispheric cyst"), distended interhemispheric fissure, abnormal radial orientation of medial cerebral gyri extending from the roof of the third ventricle ("sunburst sign") and abnormal branching of anterior cerebral artery (Figure 8.) (Penny, 2006; Atlas *et al*, 1985; Byrd *et al*, 1990).



a b c

Fig. 8. Agenesis of the corpus callosum in the sagittal planes (A) and coronal planes; (B and C).

Color Doppler scan showing the absence of the corpus callosum and abnormal course of the pericallosal artery (Figure 9.). (Schell-Apacik *et al,* 2008). Lipoma of the corpus callosum is demonstrated as a highly echogenic mass in the region of the corpus callosum.



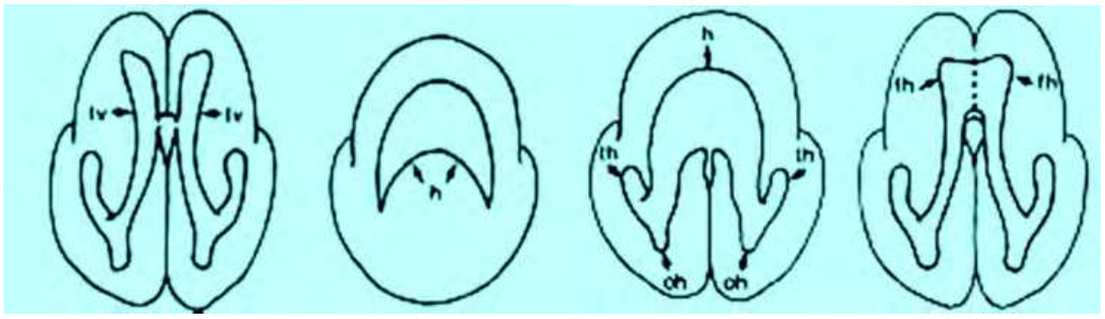
Fig. 9. Sagittal color Doppler scan shows the agenesis of the corpus callosum.

Agenesis of the corpus callosum may be a completely asymptomatic (found incidentally) or with subtle developmental deficits and severe neurologic problems, such as seizures, intellectual impairment, and psychosis. However, these conditions are believed to be caused by abnormalities in associated cerebral and chromosomal anomalies rather than in the corpus callosum per se (Goodyear *et al,* 2001). Hence, prognosis is determined primarily by the underlying or associated malformations. Studies of persons with isolated agenesis of the corpus callosum without other abnormalities show that some have normal intelligence, while others are developmentally delayed (Taylor *et al*, 1998). Complete agenesis has a worse prognosis than partial agenesis.

5. Holoprosencephaly

Holoprosencephaly is a heterogeneous entity of CNS anomalies caused by the impaired midline cleavage of the forebrain (prosencephalon) into the right and left hemispheres, and the malformation of the diencephalon, telencephalon, olfactory, and optic bulbs (Volpe, 2001).

Holoprosencephaly is graded according to the severity of the brains anomaly as alobar, semilobar and lobar (Figure 10.)(Peebles, 2001).



a b c d

Fig. 10. Schematic drawing of the normal neonatal brain (A), alobar holoprosencephaly (B), semilobar holoprosencephaly (C) and. lobar holoprosencephaly (D).

In alobar holoprosencephaly, the most severe form, the cerebral hemispheres are fused and enclose a single prosencephalic ventricle. There is a complete failure of cleavage of the forebrain into two hemispheres. It results in a single ventricular cavity with fusion of thalami, absence of corpus callosus, falx cerebri, optic tracts and olfactory bulbs. Partial cleavage results in semilobar holoprosencephaly, with posterior separation of the cerebral hemispheres, variable degrees of fusion of the thalami and absent olfactory bulbs and corpus callosus. In lobar holoprosencephaly, the abnormalities may be confined to absence of the corpus callosus and fusion of the lateral ventricles and cingulate gyrus. The two hemispheres are separated anteriorly and posteriorly. Because of a mechanism of reciprocal induction between the brain and the skull, the facial structures are also abnormal (Edison & Muenke, 2003). The severity of the facial malformation reflects the severity of the intracranial anomalies and include: cyclopia (median monoophthalmia, synophthalmia or anophthalmia with proboscis), cebocephaly or« monkey head », (ocular hypotelorism and a blind single nostril nose), ethmocephaly (ocular hypotelorism with proboscis) and median cleft lip.

Holoprosencephaly is found in several syndromes, including Meckel-Gruber syndrome, holoprosencephaly-fetal akinesia syndrome and Steinfield syndrome (Cho *et al,* 2005). The

most frequently associated CNS anomalies are microcephaly, macrocephaly, and Dandy–Walker malformations. Associated extra-cranial abnormalities are congenital heart defects, renal dysplasias, omphalocele and polydactyly.

The incidence holoprosencephaly is about to 0.6-1.9 per 1000 births, but 4 per 1000 in embryos. Half of these are associated with trisomy 13. Holoprosencephaly occurs in about 70% of the patients with trisomy 13 (Roessler & Muenke, 1998). The sex distribution shows a female predominance. The risk of recurrence depends of the basis for the actual condition, such as chromosome defect or syndrome. In the cases without chromosomal abnormalities, the recurrence risk is estimated to be 6%.

The etiology of holoprosencephaly is heterogeneous and not completely known. Most cases are sporadic and environmental, and genetic factors have all been implicated as possible causes (Muenke & Beachey, 2000). This is probably due to mutations in the gene for the sonic hedgehog morphogen and genes that encode its downstream intracellular signaling pathway (Wallis & Muenke, 2000). There is also some evidence for a defect in the cholesterol biosynthesis. Holoprosencephaly in association with extra cephalic malformations suggests aneuploidy, particularly trisomy 13. Familial holoprosencephaly is known. It can be inherited in an autosomal dominant fashion with varied penetrance, or as an autosomal recessive. In addition to the genetic component to holoprosencephaly , environmental factors are also critical. In experimental animal studies, holoprosencephaly has been induced by teratogenic agents (retinoic acid, ethanol). An association with maternal infectious (cytomegalovirus, toxoplasmosis), conditions such as gestational diabetes have also been reported.

The ultrasound of alobar holoprosencephaly is characteristic and shows a large central echo-free monoventricular cavity surrounded by a varying amount of residual cortical mantle. No midlines structures are visible. The infratentorial structures are usually present with fusion of the thalami on the midline. The semilobar holoprosencephaly is characterized by the presence of rudimentary lateral ventricles with sketchy posterior horns, and a more developed cortex, partial development of the interhemispheric fissure and of the falx cerebri, which is present only posteriorly and partial fusion of the thalami (Figure 11.). The lobar holoprosencephaly has a well developed interhemispheric fissure, partial fusion of the frontal horns with the third ventricle, hypoagenesis of the corpus callosum and the cavum septum pellucidum is absent.

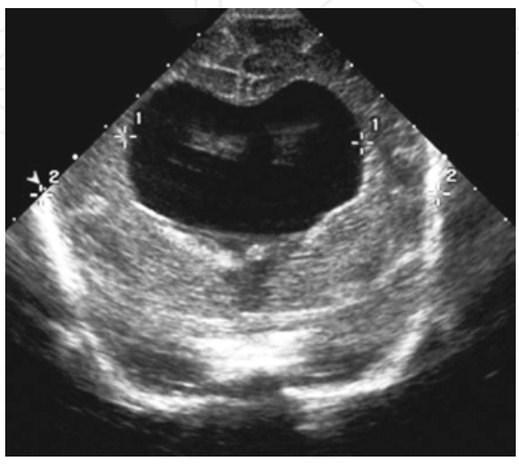


Fig. 11. Coronal scan shows the semilobar holoprosencephaly.

Prognosis depends on the form of holoprosencephaly. The severe forms are incompatible with prolonged survival. In the lobar type, the prognosis is less well defined, but mental retardation, olfactory and visual anomalies are often present Termination of pregnancy can be offered for the severe cases holoprosencephaly (semi-lobar, alobar).

6. Hydranencephaly

Hydranencephaly is characterized by the absence of the cerebral hemispheres, an incomplete or absent falx and a huge saclike structure containing cerebral spinal fluid covered by leptomeninges and dura. The brain stem is usually present, although the basal ganglia and cerebellum may be smaller than normal. The presence of the falx and of the cranial nerves demonstrates that the hemispheres have developed but have subsequently been destroyed (Dixon, 2005).

Etiology of this disorder includes: bilateral occlusion of the internal carotid or middle cerebral arteries, necrotizing vasculitis caused by infection (congenital cytomegalovirus, toxoplasmosis and herpes simplex infections), diffuse hypoxic-ischemic brain necrosis based on fetal hypoxia, leukomalacia formed by confluence of multiple cystic cavities and thromboplastic material from a deceased co-twin. The most accepted hypothesis to explain this particular lesion is interruption of the blood supply in early pregnancy (Barkovich, 2005). The occlusion of internal carotid arteries results in ischemic insult of the areas supplied by anterior and middle cerebral artery. There is variability in the extent of destruction of the cerebral hemispheres. Destruction may be complete or may spare portions of the temporal and occipital cortex. Liquefaction of the brain tissue in the area involved (usually the hemispheres), with replacement of the neural tissue by CSF and preservation of the membranes. Blood supply for the posterior brain fossa stays intact which explains the presence of brainstem and cerebellum

Hydranencephaly is a rare destructive brain lesions with prevalence to 0.1-0.2 in 1000 newborns. Hydranencephaly is found in 0.2% of infant autopsies. Recurrence risk is unknown. Aside from consequential arthrogryposis, hydranencephaly has been associated with syndromes including renal aplastic dysplasia, polyvalvular developmental heart defect, porencephaly, microcephaly and with trisomy 13 (Bendon *et al,* 1987). Familial cases are rare.

On ultrasound, hydrancephaly presents as a large cystic mass filling the entire cranial cavity with absence or discontinuity of the cerebral cortex (Figure 12.). Falx cerebri is partially missing or absent and brainstem is preserved. The pused and continuous color Doppler US show abnormal pathway and occlusion of the anterior cerebral artery crawling under the skull (Bernard *et al,* 2002; Stevenson *et al,* 2001).

The most common diagnostic problem is differentiation among hydranencephaly, extreme hydrocephalus, alobar holoprosencephaly and porencephaly. With extreme hydrocephaly, alobar holoprosencephaly or porencephaly, these structures should still be surrounded by a rim of cortex, and the choroid plexuses should be normally visible. Magnetic resonance imaging (MRI) and evoked potentials may serve as an additional means for confirming the ultrasound diagnosis (Hanigan & Aldrich, 1988). Diagnosis can be done prenatally by ultrasound (Lam & Tang, 2000).



Fig. 12. Sagittal scan show sthe typical features of hydranencephaly.

The prognosis is universally very poor and incompatible with post-natal life. Hydranencephaly is associated with severe psychomotor delay, nystagmus, optic atrophy, epilepsy, and hypothermia. Survival may last several months if an intact hypothalamus permits thermoregulation, but most die in the first two years of life. It has been suggested termination of pregnancy when an antenatal diagnosis of hydranencephaly is made.

7. Schizencephaly

Schizencephaly is an uncommon CNS congenital disorder of neuronal migration, characterized abnormal cleft by brain (Oh *et al,* 2005). The cleft can be localized anywhere on the brain, but they are usually localized on the perisylvian regions. The cleft can be unilateral or bilateral and be either symmetric or asymmetric. The clefts may extend through the entire hemisphere from the ependymal lining of the lateral ventricles to the pial surface covering the cortex of some part of the brain. The gray matter lining can be dysplastic. There are two types of schizencephaly:

Type I: The clefts can be unilateral or bilateral and may be closed (fused lips). In closed-lip, the cleft walls are in apposition, causing obliteration of the CSF space within the cleft.

Type II: The clefts can be unilateral or bilateral and may be separated (open lips). In open-lips, the clefts walls are separated. The CSF fills the cleft from the lateral ventricles to the subarachnoid space that surrounds the hemispheres. The ventricle system may be enlarged, particularly with the open lip form of schizencephaly.

Schizencephaly has an extremely rare prevalence, with an unknown incidence. There is neither sex nor race predilection. Schizencephaly type II is more frequent than schizencephaly type I. Different CNS anomalies can be associated with schizencephaly: gray-matter heterotopias, polymicrogyria, arachnoid cysts, microcephaly, agenesis of the corpus callosus (Briellmann *et al*, 1998; Hayashi *et al,* 2002). The septum pellucidum is absent in 50-85 % of the patients and may coexist with septo-optic dysplasia. Some individuals affected by schizencephaly, may have an excessive accumulation of CSF in the brain and caused ventriculomegaly and the hydrocephaly with macrocrania.

Etiology of schizencephaly remains unclear, some environmental events have been proposed. No specific prenatal events have been identified, but genetic, toxic, metabolic, vascular of infectious etiology (congenital cytomegalovirus infection) can be responsible (Montenegro *et al,* 2002; Iannetti *et al,* 1998). Schizencephaly have an autosomal dominant inheritance with incomplete penetrance and variable expression. Familial cases have been reported, suggesting a possible genetic origin within a group of neuronal migration disorders (Guerrini & Carrozzo, 2001). Recent studies have linked schizencephaly with a mutated gene called EMX2 homeobox gene (Guerrini & Carrozzo, 2001; Granata et al, 1997). If the gene EMX-2 is missing or defective, nerve cell growth and migration will not occur normally and lead to the formation of the clefts associated with schizencephaly.

Two theories are currently accepted. One argues a failure in neuronal migration from the germinal matrix, while the other argues a post-migrational vascular insult (Montenegro *et al,* 2002; Oh *et al,* 2005). Schizencephaly results from an early, focal destruction of the germinal matrix and surrounding brain, before the hemispheres are fully formed. Schizencephaly can occur due to an abnormal neuronal migration from the germinal matrix zone. According to other authors, schizencephaly and polymicrogyria are the result of the same cortical damage, because of the frequent association of an unlayered cortex lining surrounding the cleft. Schizencephaly would be an extreme variant of cortical dysplasia in which the infolding of the cortex extends all the way into the lateral ventricles.

Schizencephaly may be suspected by the appearance of focal ventricular dilatation and by visualization of gray matter lined cleft on ultrasound (Hayashi *et al,* 2002). This space is filled with CSF. In unilateral schizencephaly, the clefts is only on one side of the brain, while in bilateral schizencephaly is on both sides (Figure 13.). The septum pellucidum is absent in most patient with schizencephaly. MRI is the best method to differentiate schizencephaly from porencephaly and arachnoid cyst (Hayashi *et al,* 2002; Liang *et al,* 2002).



a b

Fig. 13. Coronal scan (A) and axial scan (B) show the typical features of bilateral schizencephaly.

The clinical features of schizencephaly are extremely variable. Usually the severity of these symptoms is related to the extent of cortex involved in the defect and associated CNS anomalies (Denis *at al* 2000; Hayashi *et al,* 2002). Children with unilateral clefts have often hemiparesis, but may also have mild-to-moderate developmental delay. Children with

bilateral clefts have severe mental and motor impairments, early onset of epilepsy and frequently blindness, deafness. Sometimes, closed-lip schizencephaly may not present clinically until later during the childhood and may live to early adulthood.

8. Lissencephaly

Cerebral cortical development is an extremely complex process, comprising three major, but overlapping, steps: cell proliferation, neuronal migration and cortical organization. Neuronal migration disorders (also, and better, called cortical developmental anomaly) are caused by abnormal proliferation, migration, and organization (lamination, gyration, and sulcation). Lissencephaly is a rare cortical developmental disorder, with reduced or absent brain gyri, which is caused by abnormal neuronal migration in the neocortex.

The incidence lissencephaly is unknown but rare. There is female predilection. Lissencephaly have been associated with deletion of a number of genes on chromosome 17p13, including *LIS1*. Identification of *LIS1* as the causative gene for lissencephaly did not come until 1993, and the role of *DCX* in both lissencephaly and subcortical band heterotopia was not determined until 1998. *DCX* is located on the long arm of the X chromosome and therefore is inherited in an X-linked dominant form, with female subjects showing a milder phenotype (subcortical band heterotopia) than male subjects (anterior greater than posterior lissencephaly). If de novo deletion or translocation occurs, the recurrence risk is low. If the translocation is inherited from one parent (who has a balanced translocation), the recurrence risk may be as high as 25%.

Lissencephaly is characterized by agyria, accompanied or not by pachygyria, minimal or no ventriculomegaly, and characteristic dysmorphic features (Verloes *et al,* 2007). The most frequently associated anomalies are duodenal atresia, urinary tract abnormalities, congenital heart defects, cryptorchidism, inguinal hernia, clinodactyly, polydactyly, and ear anomalies may be found. The classification of lissencephaly has undergone significant revision in the last decade, as a result of recent discoveries regarding the molecular biological basis of such malformations, and findings on MRI and autopsy. There are three main groups of lissencephaly (Barkovich *et al,* 2001).

Group A lissencephaly (or classical lissencephaly) is characterized by agyria with or without pachygyria, a wide cortical mantle and minimal or no hydrocephalus. In classical lissencephaly (agyria/pachygyria), the normal six-layered cortex is replaced by an abnormally thick four-layered cortex and characterized by simplified or absent gyration. The incidence of all forms of type I lissencephaly is around 1 in 100,000 births. The subtypes of group A lissencephaly are:

1. Miller-Dieker syndrome is associated with a deletion at the chromosome 17p13.3 locus. This syndrome has lissencephaly combined with dysmorphic facial features and other possible associated CNS anomalies (dysgenesis of the corpus callosum, ventriculomegaly, midline calcifications, and mild cortical cerebellar dysplasia). Microcephaly is common. Associated abnormalities include heart malformations, omphalocele, kidney dysplasia, and genital anomalies). Transverse palmar creases and clinodactyly are common. Among extracranial abnormalities, the most common is intrauterine growth restriction.

2. In Norman-Roberts syndrome, no abnormal karyotype is fond. This syndrome is autosomal recessively inherited. It is a type I lissencephaly with sloping forehead and other minor facial features described in a consanguineous family.

3. Isolated *type I* lissencephaly is not associated with deletion at the chromosome 17p13.3 locus or abnormalities limited to the *LIS1* gene. Patients with isolated lissencephaly do not have other congenital anomalies or severe dysmorphic features.

Group B lissencephaly (or type II) is characterised by global disorganisation of cerebral organogenesis with an uneven cortical surface Lissencephaly, type II typically has hydrocephalus and additional serious CNS defects. The subtypes of group B lissencephaly are:

1. HARD+/-E syndrome, an acronym for Hydrocephalus, Agyria, Retinal dysplasia, Encephalocele (Walker-Warburg syndrome), is an autosomal recessive lethal disorder. Associated abnormalities include other serious CNS malformations such as dysgenesis of the corpus callosum, cerebellar dysplasia with Dandy-Walker malformation, and white brain substance atrophy are found.

2. Cerebro-oculomuscular syndrome with congenital muscular dysplasia is possibly a variant of the HARD+/-E syndrome, and is supposed to be autosomal recessively inherited. Other subtypes of type II lissencephaly are possible.

Group C lissencephaly is found in lissencephaly associated with Neu-Laxova syndrome which is a lethal autosomal recessive inherited disorder consisting of growth retardation, microcephaly, lissencephaly, dysgenesis of the corpus callosum, intracranial calcifications, cerebellar hypoplasia, facial dysmorphism, microphthalmia, exophthalmus, cataracts, absent eyelids, hydrops, ichthyosis, contractures of extremities and syndactyly.

Lssencephaly may be suspected if appear a smooth gyral pattern, ventriculomegaly, and a prominent subarachnoid space on ultrasound (Barkovich *et al,* 2001) (Figure 14.). The progressive microcephaly and failure of development of both sulci and gyri (which in normal conditions is well defined from 26 to 28 weeks) are suggestive of lissencephaly (Fong *et al,* 2004). MRI may be better able to detect the pachygyric appearance of the cerebral cortex and subcortical band heterotopia (Garel et al, 2001; Levente, 2005).

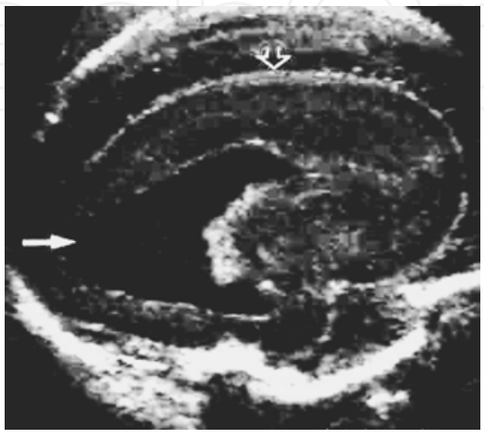


Fig. 14. Coronal scan shows the typical features of lissencephaly.

The prognosis of lissencephaly is universally poor, regardless of etiological type, and death occurs usually within the first 2 years of life. Usually severe mental retardation affects these patients. Failure to thrive, infantile spasms, and seizures are also expected.

9. Porencephaly

The term 'porencephaly' includes every type of destructive brain lesion with cavitary character, i.e. a fluid-filled spaces within the brain that commonly communicates with the ventricles, subarachnoid spaces, or both. It involves the destruction of previously developed brain tissue, with subsequent cavity formation. It may be isolated or associated with ventriculomegaly. Some authors consider two types of porencephaly.

Type I porencephaly or encephaloclastic porencephaly is due to parenchymal damage followed by liquification/reabsorption, resulting from an insult (ischemia, hemorrhage, etc.) during the 3rd trimester. It is more frequent and usually unilateral. It has a round or irregular shape.

Type II porencephaly or schizencephalic porencephaly, which is usually bilateral, caused by abnormal neural migration and cortical organization. It is best considered separately as a primary developmental abnormality.

Etiology of porencephaly disorder includes: ischemic episode, trauma, demise of one twin, intercerebral hemorrhage and infection (Scher *et al,* 1991). This occurs when the immature brain has a propensity to dissolution and cavitations (due to high water content or a deficient astroglial response). The timing of ischemic injury (maybe as early as the 2nd trimester) is closely related to porencephaly and hydranencephaly.

Porencephaly is a rare destructive brain lesion with prevalence to 0.1-0.2 in 1000 newborns. Risk of non-chromosomal syndromes is low. Type II porencephaly may be associated with orofaciodigital syndrome type I, and other CNS anomalies. The most frequently associated anomalies are hydrocephalus.

On ultrasound, porencephaly appears as a unilateral cystic lesion, usually communicating with the ipsilateral ventricle and/or the subarachnoid space (Figure 15.). A porencephalic cyst never causes a mass effect, which is observed with arachnoid cysts and other cystic

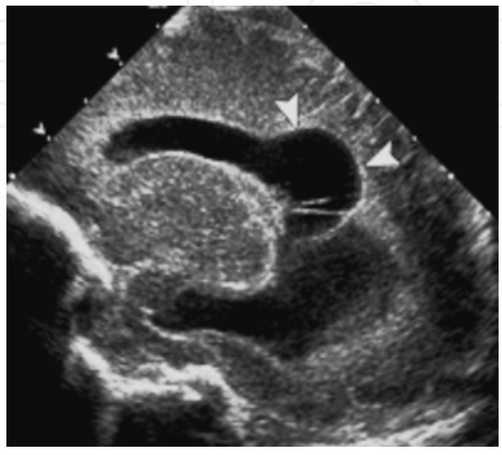


Fig. 15. Sagittal scan shows the typical features of porencephalic cyst.

mass lesions. This condition is an acquired brain insult and should be differentiated from schizencephaly of migration disorder. The cystic walls and the content of the cyst may vary according to the gestational age at which the insult occurs. If it is secondary to hemorrhage, it is possible to visualize a hyperechoic focus evolving into an anechoic CSF-filled cyst. Diagnosis can be done prenatally by ultrasound (Meizner & Elchalal, 1996).

Prognosis is variable, depending on the timing and extent of the lesion. Epilepsy psychomotor retardation and cerebral palsy often occur. In type II, due to the bilaterality of the lesion and the tendency to be part of a syndrome, the prognosis is worse. A ventriculoperitoneal shunt should be applied if hydrocephalus progresses.

10. Arachnoid cysts

Arachnoid cysts are congenital lesions of the arachnoid membrane that expand with CSF secretion. They exist between the brain substance and dura and that may exist separately as a loculated accumulation between two arachnoid membranes or may communicate with the subarachnoid space. They represent 1% of all intracranial masses in newborns and they are found at 0.5% of autopsies. Arachnoid cysts are fluid-filled cavities lined completely or partially by the arachnoid membrane. The cysts are mostly single, but two or more can occasionally be observed. Arachnoid cysts have been found anywhere in the CNS, including the spinal canal. The most frequent locations are the surface of the cerebral hemispheres in the sites of the major fissures (sylvian, rolandic, and interhemispheric), the region of sella turcica, the anterior fossa, and the middle fossa (Nakamura *et al,* 2001). Less frequently, they are seen in the posterior fossa. Arachnoid cysts may increase or decrease in size.

Arachnoid cysts have been associated with hydrocephalus, Aicardi syndrome, glutaric aciduria type I, and unbalanced X,9 translocation. Interhemispheric cysts are often associated with dysgenesis of the corpus callosum (Hirohata *et al,* 1992). Recurrence risk is unknown.

Intracranial arachnoid cysts may be primary (congenital) or secondary (acquired). Congenital types are believed to be formed by maldevelopment arachnoid membranes and do not freely communicate with subarachnoid space. Acquired types are formed as the result of hemorrhage, trauma, and infection and often communicate with subarachnoid space. Arachnoid cysts have the potential to grow as the result of some communication with the subarachnoid space. The accumulation of fluid is believed to result from a ball valve mechanism. Furthermore, a choroid plexus-like tissue within the cyst wall, which secretes CSF and thus contributes to a progressive distension of the lesion, has been reported by several investigators. It contains clear cerebrospinal fluid and has been diagnosed prenatally by ultrasound.

On ultrasound, arachnoid cysts present as a well-defined anechoic cystic structure with adjacent mass effect. The primary manifestation of an arachnoid cyst is a localized fluid collection occasionally causing hydrocephallus. Large arachnoid cysts may obstruct the circulation of CSF, leading to secondary obstructive hydrocephalus. The cyst can obstruct the foramen of Monro, displace the aqueduct posteriorly, and block the basal cisterns. Application of color Doppler will not demonstrate high flow (Figure 16.).

The differential diagnosis from other cystic lesions may be difficult. Porencephaly is often associated with ventriculomegaly, communicates with the ventricles and follows a vascular

distribution. Brain tumors are usually solid or of mixed echogenicity and are rarely completely cystic. Posterior fossa arachnoid cysts should be differentiated from Dandy-Walker malformation. The main criterion in these cases is the integrity of the cerebellar vermis in arachnoid cysts. Suprasellar arachnoid cysts are rounded and should be differentiated from a large third ventricle. The dilated third ventricle appears oval with tapered edges posteriorly when aqueductal stenosis is present. An arachnoid cyst in the midline should be differentiated from dysgenesis of corpus callosum with an associated interhemispheric cyst. In cases of corpus callosal dysgenesis, the enlarged third ventricle is high in location at the level of the lateral ventricles, and the ventricular atria are prominent. A vein of Galen aneurysm, is a midline occipital lesion with characteristic Doppler flow.

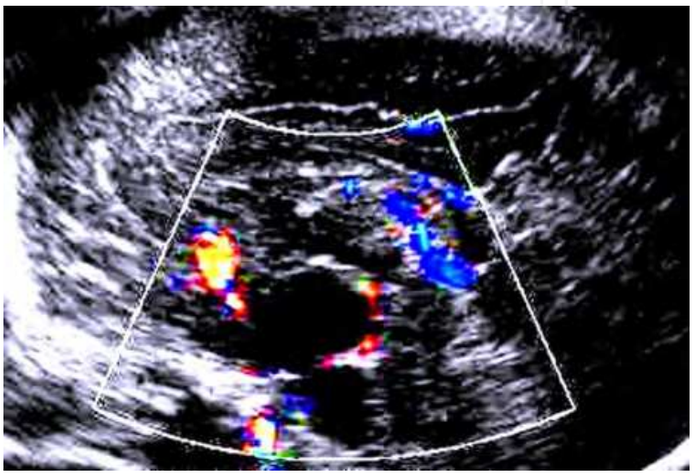


Fig. 16. Sagittal scan shows the typical features of arachnoid cysts.

Prognosis is generally good (Elbers & Furness, 1999). In many cases, arachnoid cysts are asymptomatic, but they may cause epilepsy, mild motor or sensory abnormalities, or hydrocephalus. Depending on the location and extent of the lesion, these cysts can be resected or shunted. Conversely, suprasellar arachnoid cysts are rare, representing approximately 10% of intracranial arachnoid cysts, however, they have a propensity to become symptomatic and they may manifest with hydrocephalus, visual impairment, and endocrine dysfunctions (typically precocious puberty).

11. Posterior fossa cystic lesions

Despite decades of knowledge of the existence of posterior fossa cystic anomalies and efforts to understand their pathogenesis, there is little consensus about how these malformations occur and how they cause clinical symptoms/signs (Altman, 1992; Barkovich *et al,* 1989).

However, their differential diagnosis can be particularly difficult because the recognition of the subtle anatomic features that differentiate them may be challenging or sometimes impossible.

Some cysts are related to massive dilatation of the fourth ventricle, others to persistence of embryonic structures, such as Blake's pouch, others to malformative dilatation of subarachnoid spaces, and others to true arachnoid loculations.

The mainstay of the diagnosis is represented by the assessment of a number of direct and indirect signs, including the following: the relationship of the cyst with the fourth ventricle and subarachnoid spaces; the morphology, position and biometry of the vermis and the cerebellar hemispheres, association with hydrocephalus; the size of the posterior fossa and the position of the tentorium.

11.1 Mega cisterna magna

The cisterna magna is the basal cistern behind and below the cerebellum. Mega cisterna magna is defined as a cystic posterior fossa malformation characterized by an intact vermis, an enlarged cisterna magna, freely communicating with the perimedullary subarachnoid spaces, absence of hydrocephalus, and a normal size of the fourth ventricle. The tentorium cerebelli is superiorly displaced in almost 10% of cases.

Mega cisterna magna occurs in approximately 1% of all brains imaged postnatally. Mega cisterna magna has been associated with infarction, inflammation, and infection, particularly cytomegalovirus, as well as with chromosomal abnormalities, especially trisomy 18. In the absence of other findings to suggest a posterior fossa lesion, a mega cisterna magna is unlikely to be clinically significant.

On ultrasound, normal cisterna magna characteristically measures 3–8 mm when measurements are taken in the midsagittal plane from the posterior lip of the foramen magnum to the caudal margin of the inferior vermis (Goodwin & Quisling, 1983). Ultrasound examination reveals a cystic posterior fossa malformation characterized by an intact vermis, an enlarged cisterna magna, absence of hydrocephalus, and a normal size of the fourth ventricle (Figure 17.). The extent of the CSF collection is variable; it may remain purely infravermian or it may extend far beyond the normal borders of the cisterna magna laterally, posteriorly, and superiorly, reaching in some cases the quadrigeminal plate cistern. The tentorium are usually in normal position.



Fig. 17. Sagittal scan shows the typical features of Mega cisterna magna.

Prognosis is commonly favorable if Mega cisterna magna is isolated. In syndromic conditions, the final prognosis is that of the underlying syndrome.

11.2 Blake's pouch cyst

The Blake's pouch is a normal, transient embryological structure (superior medullary velum), which initially does not communicate with the surrounding sub-arachnoid spaces. Subsequent spontaneous perforation of the pouch forms the foramen of Magendie. If the Blake's pouch fails to perforate, CSF accumulates and determines the fingerlike expansion Blake's pouch cyst within the posterior fossa and produce hydrocephalus.

Some authors put forward the theory that Blake's pouch cyst and retrocerebellar arachnoid cysts are the same entity because at some stage the communication with the fourth ventricle is lost and contact with the developing arachnoid matter is made (Strand *et al,* 1993). Another authors clearly distinguish between Blake's pouch cysts and retrocerebellar arachnoid cysts although they recognize differentiation of the two on imaging is difficult and can only be resolved on histological analysis (Calabro *et al,* 2000).

Sonographically, Blake's pouch cysts is characterized by a normal but displaced cerebellar vermis, a CSF collection in the posterior fossa, consisting of the expanded and imperforated Blake's pouch widely communicating with the fourth ventricle. Ventriculomegaly/ hydrocephalus is often associated. The tentorium is usually in normal position. A normal appearance of the cerebellar vermis rules out the diagnosis of the Dandy–Walker malformation, in which the vermis is agnetic/hypoplastic and rotated counterclockwise (Calabro *et al,* 2000).

The prognosis of Blake's pouch cysts is generally good.

11.3 Dandy-Walker malformation

The term Dandy–Walker malformation was suggested to describe a malformation consisting of a cystic enlargement of the fourth ventricle associated with partial or complete agenesis of the vermis (Nelson *et al,* 2004)

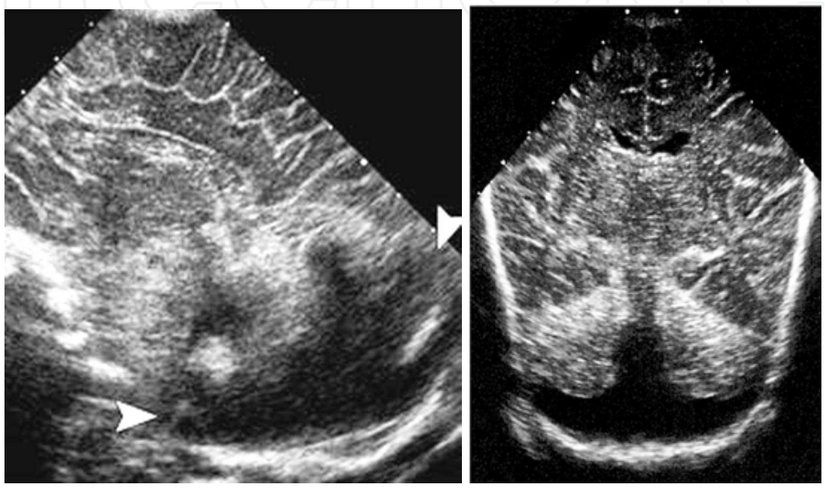
Incidence of the Dandy-Walker is about 1 in 25,000–35,000 births.

There is a high association with other CNS abnormalities (in 50–60% of cases), including failed commissuration, cortical formation malformations, midline anomalies and encephalocoeles. An association with facial clefts and other extra-CNS anomalies (especially congenital heart disease and urinary anomalies) has been described, often in the context of chromosomal and genetic syndromes. Risk of chromosomal anomalies is high, with up to 35% of cases being associated with aneuploidy, mainly trisomies 18 and 13. The most common syndromes that can be associated with the Dandy–Walker malformation are: Walker–Warburg syndrome, Meckel–Gruber syndrome, Aicardi syndrome and Neu–Laxova syndrome.

The Dandy–Walker malformation is a result of defective development of the structures originating from the rhomboencephalic roof (Calabro *et al,* 2000; Nelson *et al,* 2004). Failure of assimilation of the area membranacea anterior, leading to anomalous development of the fourth ventricle, atresia of the foramen of Magendie and sometimes the foramen of Luschka. The cystic dilatation of the fourth ventricle fills the posterior fossa and extends into cisterna magna, which is compressed between the dilated fourth ventricle and the dura mater. Ventriculomegaly develops in up to 80% of cases. The high insertion of the tentorium

encountered in the Dandy-Walker malformation is considered an indicator that the malformation occurred before the end of the embryonic period.

On ultrasound, the Dandy–Walker malformation is characterized by an expansion of the posterior cranial fossa with upward displacement of the tentorium, a cystic dilatation of the fourth ventricle, and partial or complete vermian agenesis (Figure 18.). In addition, when present, the cerebellar vermis is rotated counter clockwise. Some cases of Dandy–Walker malformation show a partial agenesis/ hypoplasia, whereas others feature vermian dysplasia.



a b

Fig. 18. Sagittal scan (A) and coronal (B)show the typical features of Dandy–Walker malformation.

Prognosis is poor when associated with other CNS anomalies and chromosomal and genetic syndromes (Klein *et al,* 2004). Isolated the Dandy–Walker malformation forms have a better intellectual prognosis and lower mortality

Less-pronounced malformations are often termed Dandy-Walker varianta.

The Dandy–Walker variant has a very similar appearance but there is a lesser degree of hypoplasia of the cerebellar vermis. The foramen of Magendie is, however, patent. The fourth ventricle is less dilated. The Dandy–Walker variant is a mild form of the Dandy–Walker malformation or represents a generalized form of cerebellar hypoplasia. However, the demarcation between classic Dandy-Walker malformation and Dandy-Walker variant is vague, and thus the term Dandy-Walker continuum is more appropriate. To further simplify these lesions, the definition of Dandy-Walker malformation has been modified and Blake's pouch cyst has been included in the "Dandy-Walker continuum".

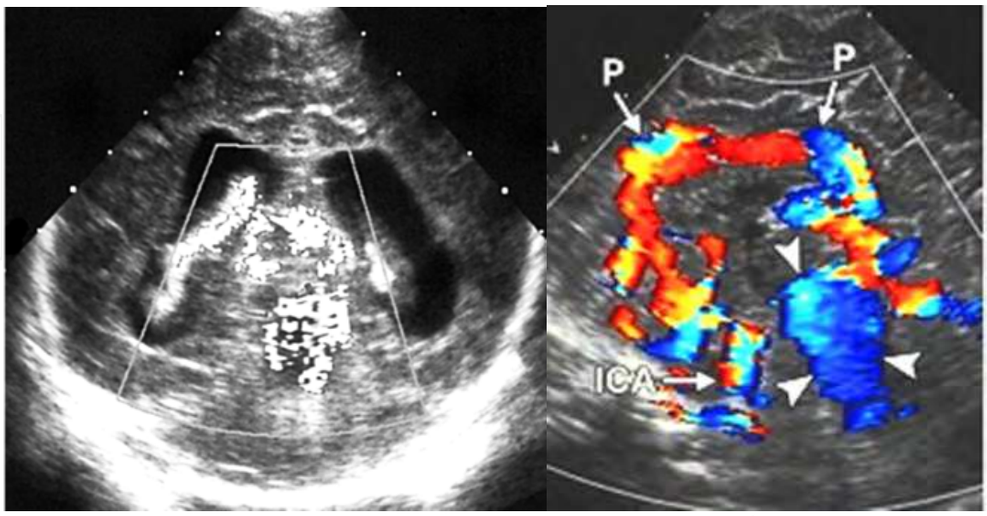
12. Vein of Galen aneurysm

The vein of Galen is part off the venous sinus complex which drains blood from brain. Aneurysm of the vein of Galen is a complex arteriovenous malformation consisting of multiple communications between the system of the vein of Galen and the cerebral arteries

(carotid and/or vertebrobasiliar systems). These vessels are located in the brain deeply and posteriorly above the pineal gland, in the subarachnoid space called "cistern of the great cerebral vein of Galen". There three types described: arteriovenous fistula, arteriovenous malformation with ectasia of the vein of Galen and varix of the vein of Galen (Raybaud *et al,* 1989). The vein of Galen malformation is a form of embryonic arteriovenous shunt. Other venous anomalies, such as anomalous dural sinuses and sinus stenosis, are commonly present in association with vein of Galen malformation.

Incidence of aneurysm the vein of Galen is rare. It represents 1% of all vascular brain malformations. It is more common in males than females. It is often associated with other more extensive cerebral abnormalities. It may be associated with secondary hydrocephalus due to compression of the aqueduct and with high-output heart failure and non-immune hydrops due to the arteriovenous fistula (Brunelle, 1997). Severe high-output cardiac failure is caused by a marked increase of cardiac preload from venous return of the brain due to the 'steal' phenomenon. The 'steal' phenomenon, with diversion of blood from the parenchyma to the aneurysm, may further result in brain infarcts and periventricular white matter lesions.

Ultrasound examination reveals a large echo-free supratentorial cystic structure with high velocity flow on Doppler examination (Figure 19.). This lies posterior to the third ventricle, and may extend asymmetrically across the midline. Size of this cystic structure depends on volume of shunt. The sagittal sinus is reported as dilated in most cases. The feeding arteries are difficult to analyze, but a tortuous network of dilated arteries is usually visible in the region of the malformation. Demonstration of blood flow in the cystic structure enables the diagnosis of an aneurysm of the vein of Galen to be made, as opposed to that of an abnormality of other intracranial midline structures, for example arachnoid or porencephalic cyst, Dandy–Walker malformation or intracerebral hematoma. However, when a clot has formed, it may be iso-or even hyperechoic (Vijayarghavan *et al,* 2006).



a b

Fig. 19. Coronal scan (A) and sagittal scan (B) show the typical features of the vein of Galen malformation.

Prognosis of aneurysm the vein of Galen is poor when cardiac failure and hydrops is present. Risk of intrauterine or early neonatal death due to congestive heart failure, requires agressive postnatal care. Although the vein of Galen aneurysms may become symptomatic in the elderly, they are more typically diagnosed in the neonatal period. The common clinical features in the neonate are cardiomegaly with congestive heart failure and increased intracranial pressure with hydrocephaly or cranial bruit. Focal neurological deficit, seizures and hemorrhages are less common findings. If possible, method of treatment is emergency embolization or surgery. However, there are some reports of spontaneous thrombosis and calcification of aneurysm of the vein of Galen (Nikas *et al,* 1999; Chapman & Hockley, 1989).

13. Neural tube defects

Neural tube defects are the most frequent CNS malformations and amount to about 1–2 cases per 1000 births. There have been many reported remarkable reductions in the prevalence of neural tube defects after the use of folic acid supplementation and fortification, although some have reported no decline in the anencephaly rate. Neural tube defects includes different anomalies deriving from failed closure of the neural tube between the 3rd and the 4th week of development, the best known being anencephaly, cefalocele, and spina bifida.

13.1 Anencephaly

Anencephaly results from failure of anterior neural tube closure and occurs before 24 days of gestation. Anencephaly is a lethal anomaly characterized by the absence of cerebral hemispheres and cranial vault. Most of the cranial vault is absent. It is the most common CNS malformation. Its incidence is 0.1 in 1000 births. 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. The risk of recurrence of anencephaly is 5% to 13%. Anencephaly is associated with myelomeningocele, microcephaly and amniotic band syndrome. Extra-cranial abnormalities occur in some cases and included omphaloceles and clubfoot.

Anencephaly has a multifactorial etiology. Genetic factors seem important because of familial incidence, whereas geographic variation suggests an environmental cause. An increased incidence of anencephaly and other neural tube defects occur in women who have diabetes during pregnancy. Also, women who take valproic acid for a seizure disorder are at increased risk for anencephaly if their medication has been consumed prior to conception or during the first trimester of pregnancy. The most widely accepted theory is that in most cases, because of a failure of development of the cranial vault bones, the encephalic structures, covered only by the meninges, are in time subject to extensive destruction, with consequent transformation of the encephalon into a mass of soft tissue adhering to the base of the cranium (cerebral–vascular area).

On ultrasound, the anencephalic foetus have a typical froglike appearance (bulging eyes, cleft lip or palate, a large tongue, and a very short neck) (Chatzipapas & Whitlow, 1999). This anomaly is incompatible with life. Approximately 75% of these neonates are stillborn, and the remainder die within the first hours or days of life. Anencephalic infants are a potential source of organs for transplantation (Trugg & Fletcher, 1989).

13.2 Cephalocele

Cephalocele is usually considered to be a restricted disorder of anterior neural tube closure. It occurs before 26 days of gestation. Cephalocele is characterized by protrusion of intracranial structures through a cranial bone defect. The herniated anatomic structures can consist of meninges only (meningocephalocele) or meninges plus cerebral tissue (encephalomeningocele). Cephaloceles are defined anatomically according to their location (frontal, parietal, occipital, frontoethmoidal, etc.). Neural tissue (most often from the occipital lobe) in the encephalocele usually displays a normal gyration and underlying white matter and is connected to the brain through a narrow neck. The most common location is occipital in Europe and the USA, although frontal cephaloceles are more frequent in South-East Asia.

This is relatively high percent **(**14–18%) of chromosomal anomalies (e.g., trisomy 13 and 18). The syndromes possibly associated with cephalocele are Meckel–Gruber syndrome, amniotic band syndrome, frontonasal dysplasia and Walker–Warburg syndrome. Associated anomalies occur in up to 70–80% of cases and included agenesis of the corpus callosum, ventriculomegaly, holoprosencephaly, spina bifida and microcephaly. Among extracerebral anomalies, the most frequently associated are cardiac anomalies and skeletal dysplasias.

According to the most widely accepted theory, cephalocele is caused by a lack of fusion of the neural tube in its specific closing sites, although some authors claim that postneurulation events with anomalies of the mesenchymal induction phases of the nervous tissue are responsible for the lesion.

Ultrasound diagnosis is based on the recognition of a cystic (meningocephalocele) or complex (meningoencephalocele) formation of variable size protruding through a skull defect, often localized in the occipital region (Figure 20.). In cases where the cephalocele is located in the lower occipital region or upper cervical area, cerebellum is usually present in the encephalocele and often associated with type III Chiari malformation. Chiari III malformation is a high cervical encephalomeningocele in which the medulla, fourth ventricle, and virtually the entire cerebellum reside.



Fig. 20. Axial scan shows the typical features of occipital cephalocele.

Prognosis is depending on the dimensions and the location of the lesion, on the presence of cerebral tissue in the herniated sack, and on any association with hydrocephaly or microcephaly or other extracranial anomalies. The postnatal mortality rate varies from 30% to 50%, depending on the above-mentioned parameters. Very large lesions have an unfavorable prognosis, while small cephaloceles can be corrected surgically.

13.3 Spina bifida

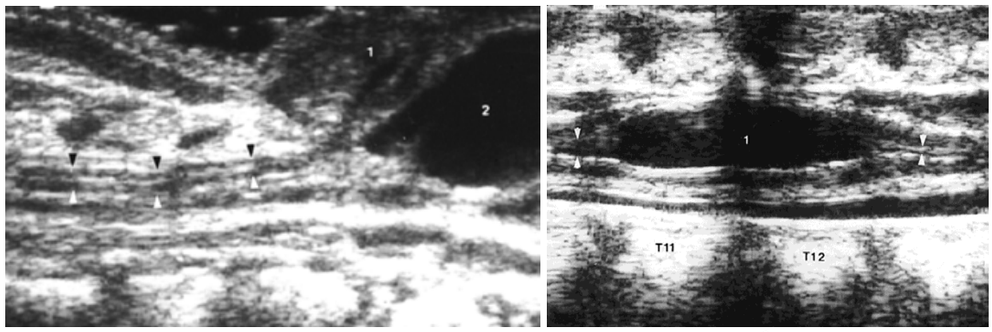
The term 'spina bifida' is still commonly used as a synonym for spinal dysraphism, although it properly refers to defective fusion of posterior spinal bony elements. The terms spina bifida aperta or cystica and spina bifida occulta were once used to refer to open spinal dysraphism and closed spinal dysraphism, respectively but have been progressively discarded. Spina bifida encompasses a broad spectrum of abnormalities. Lesions are commonly subdivides 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. This lesion is generally seen in the lower cervical or upper thoracic vertebrae. Dorsal defects are the most common. Closed spinal dysraphisms represents approximately 15% of the cases and is characterized by a small defect completely covered by skin. Closed spinal dysraphisms are considered to be disorders of caudal neural tube formation (secondary neurulation) and include distortion of the spinal cord or roots by fibrous bands and adhesions, intraspinal lipomas, epidermoid cysts, fibrolipomas, tethered cord (the most common condition), and diastematomyelia. 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. Closed spinal defects are extremely difficult to diagnose. Open spinal dysraphism is the most frequent lesion. 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 us a meningocele. More frequently, neural tissue is part of the mass, and the name myelomeningocele is used. The skin and muscles above the defect are absent. Approximately 75% of myelomeningoceles have a lumbar localization.

The incidence varies according to many factors, such as geographical area, ethnic differences, and seasonal variation. Spinal defects are more frequent in Caucasians than in Orientals or blacks. Spina bifida has a multifactorial etiology. The vast majority of cases are thought to be due to an interaction of genetic factors (chromosomal abnormalities and in single-gene disorders) with environmental factors (such as valproate exposure or maternal diabetes mellitus). Risk of chromosomal anomalies (trisomy 13, trisomy 18 and triploidy) is 8–16%. The syndromes possibly associated with spina bifida are Meckel syndrome, HARDE syndrome, Marfans syndrome and Ehlers–Danlos syndromes.

Cranial ultrasound should always be performed in neonates with spinal dysraphisms, as there may be associated a variety of intracranial abnormalities, including ventriculomegaly and hypoplasia of the posterior fossa structures. All infants with spina bifida have some degree of Arnold-Chiari type II malformation (D'Addario *et al,* 2001). Arnold-Chiari type II malformation is complex congenital anomaly of the hindbrain characterized by displacement of cerebellar tonsils, parts of the cerebellum, fourth ventricle, pons, and medulla oblongata through the foramen magnum into the spinal canal. In 95% of the cases it

is accompanied by hydrocephalus and myelomeningocele. Clubfoot may develop in a significant percentage of cases. Neonates with lumbal spinal dysraphisms should have a hydronephrosis and renal ultrasound should also be perfomed.

A larger bone and cartilage-free portals may be present at the site of the lesion on a spinal ultrasonography. A meningocele contains only CSF and no neural elements (Figure 21.a). The sac is clearly cystic and occasionally communicates directly with the extra-axial space. Myelomeningocele may be unilocular or multi-locular sacs but always contain hyperechoic nerve roots. Ultrasonography should not be performed on open lesions. Both myelomeningoceles and meningoceles are associated with a tethered low-lying spinal cord and diastematomyelia or syringomyelia. Tethering of the spinal cord occurs in 70%–90% of these neonates. If spinal cord lies posteriorly and appears fixed then tethering should be suspected. In cases in which there is a low tethered cord, the conus is low and the spinal cord is displaced dorsally. There is lack of normal cord pulsatility, and the filum terminale is thickened to over 2 mm. The thickened filum terminale may be fibrous or lipomatous. Lipomas are highly echogenic and are easily identified on sonograms. Hydromyelia or syringomyelia occurs in 40-80% of these neonates. These conditions result from disturbance of cerebrospinal fluid circulation. Hydromyelia and syringomyelia always occur cranial to the placode and may be focal or involve the entire spinal cord and spinal US shows dilatation of the central canal of the spinal cord (Figure 21.b).



a b

Fig. 21. Longitudinal scan shows the typical features of meningocele (A) and syringomyelia (B).

There is high association with ventriculomegaly and Arnold-Chiari type II malformation. Ultrasound diagnosis of the Arnold-Chiari type II malformation is based on the recognition of: ventriculomegaly, banana sign (abnormal anterior curvature of the cerebellar hemispheres), caudal displacement of fastigium of fourth ventrcle and cerebellar hemispheres, obliteration of the cisterna magna (< 2 mm), and a hypoplastic cerebellar hemispheres (Figure 22.).

Spina bifida is a serious congenital anomaly. Prognosis depend on the location and extent of the lesion (cervical and high thoracic lesions are frequently fatal), kyphoscoliosis and other major structural abnormalities. The presence of severe hydrocephaly has always been considered a poor prognostic sign. The stillbirth rate is estimated as 25%. The untreated infants die within the first few months of life. Survival rate of those treated in the immediate neonatal period approaches 40% at seven years. Clinical symptoms are variable (absent, minimal, moderate, or severe) according to the degree of neural tissue involvement. Varying

degree of paresis (often severe) of the legs and sphincter dysfunction are the major clinical signs. Intellectual and psychological disturbances are also frequently associated.



Fig. 22. Axial scan shows the tipical features of the Arnold-Chiari type II malformation.

14. Conclusions

Congenital brain anomalies are some of the most common of all congenital abnormalities These abnormalities are often evident of birth, but some brain malformations may not be immediately obvious. The neonates with dysmorphic features or abnormal neurologic behaviour may suggest cerebral malformation, and various imaging techniques are essential for fether clarification. In the neonatal period cranial US can be used as the initial modality to exclude a major structural malformation. Cranial US is non-invasive highly sensitive, safe, easily repeatable and cost effective for detecting congenital anomalies of the brain in both preterm and full-term neonates. It may provide important information regarding the anatomic location, size, and shape of congenital brain anomalies as well as their mass effect on adjacent structures. Cranial US are correlated with anatomical and pathological findings and clinical outcomes. Familiarity with the US features of congenital brain anomalies is therefore an extremely valuable tool, as it facilitates an accurate diagnosis and treatment when necessary.

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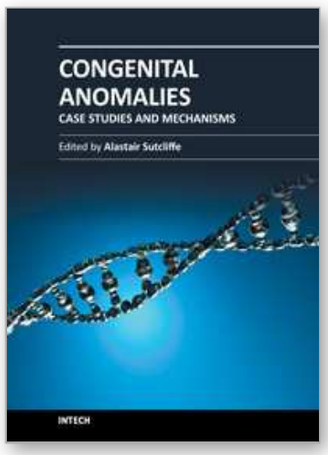
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This book is in essence a collection of essays which are state of the art in their respective areas of knowledge. They inform the reader of all sorts of mechanistic considerations when developing understanding of issues surrounding the origins of congenital abnormalities. These chapters are written by world renown authorities in this area of science and represent a wide range of expertise from a clinician perspective, through to genetic mechanisms. Unlike some books which take a formal textual, somewhat plodding way through pathophysiology here instead we have cut through chapters in which the student , or scientist or medic is lead to understand just how complex the origins can be via examples from different parts of the body. With the erudite chapters are relevant tables and other diagrams to help clarify the text . These chapters represent a starter text for the stimulus for further knowledge of what is an increasingly important area of human health.

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Phone: +86-21-62489820
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