Central Nervous System Malformations

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ABSTRACT

Ultrasound (US) is a useful tool to evaluate the normal morphology, the developmental changes, and the malformations of the fetal central nervous system (CNS). The development of the fetal CNS is a complex and continuous process progressing till the end of pregnancy and even after delivery. Although, a limited number of CNS anomalies may be suspected in the 1st trimester, the 2nd trimester is the best period of pregnancy to screen for CNS anomalies, but some malformations may be recognized only in the 3rd trimester or become evident only in the postnatal period. Screening for CNS anomalies relies on the use of the basic examination, which requires two simple axial planes on the fetal head (transventricular and transcerebellar). For a more detailed evaluation of brain malformations, an expanded fetal neurosonogram is needed, based on the use of multiple sagittal and coronal planes. The correct diagnosis of a CNS anomaly must be followed by an accurate counseling since the prognosis is varying widely.

Keywords: Fetal CNS malformations, Prenatal diagnosis, Ultrasound.

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INTRODUCTION

Central nervous system (CNS) malformations occur in 5.3 per 1,000 deliveries; their incidence is even higher if abortions and stillbirths are taken into account. The clinical consequence of these pathologies is extremely variable, ranging from transient conditions to disorders not compatible with postnatal life.¹ Most of them, however, carry a poor prognosis for their neurological sequelae. Central nervous system anomalies usually appear in low-risk population and for this reason, the only realistic approach for their prenatal diagnosis is a sonographic screening of all pregnant patients. This is usually done at 19 to 21 weeks of pregnancy. According to the guidelines of the International Society of Ultrasound in Obstetrics and Gynecology,² the evaluation of the fetal CNS includes a "basic examination" and an expanded "fetal neurosonogram."

The "basic examination" relies on two axial planes:

1. Transventricular plane showing anteriorly the frontal horns of the lateral ventricles, divided by the cavum septi pellucidum (CSP), posteriorly the atria of the lateral ventricles, almost completely filled by the echogenic choroid plexuses; at the level of the choroid plexuses the atrial width can be measured, which is normally inferior to 10 mm independently from gestational age (Fig. 1A).
2. Transcerebellar plane passing through the posterior fossa and showing the cerebellum and the cisterna magna; at this level, the transverse cerebellar diameter and the cisterna magna width can be measured (Fig. 1B). The latter is normally superior to 2 mm, but does not exceed 10 mm.

A third axial plane, called transthalamic plane, is frequently added for purpose of biometry; it shows the CSP, the thalami, and the hippocampal gyri and is used to measure the biparietal diameter and the head circumference (Fig. 1C).

The sensitivity of the basic ultrasound (US) examination in screening CNS anomalies in low-risk populations is reported as high as 80%. However, these results overestimate the diagnostic potential of US. Several CNS anomalies can be missed for different reasons: Subtle findings, late onset (such as cortical anomalies, tumors), acquired prenatal, or perinatal insults.

The expanded neurosonogram allows a more detailed evaluation of the fetal brain by using sagittal and coronal planes through a multiplanar approach obtained by aligning the transducer with the sutures and fontanelles of the fetal head. When the fetal head is deep in the maternal pelvis, a transvaginal approach can be used.³ The systematic evaluation of the fetal brain includes three sagittal and four coronal planes. The sagittal planes are the midsagittal and the parasagittal of each side of the brain. The midsagittal plane clearly shows the inter-hemispheric structures, such as the corpus callosum (CC) with its typical "C" shaped appearance, located above the CSP and cavum vergae; in the same scan the cerebellar vermis and the 4th ventricle can be seen in the posterior fossa below the tentorium (Fig. 2A). By tilting the probe laterally, the parasagittal plane is obtained showing the lateral ventricle with the choroid plexus inside (Fig. 2B), the periventricular tissue, and the brain surface.

By rotating the transducer 90° the coronal sections are obtained, which can be performed at different levels,

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Figs 1A to C: Basic examination of the fetal brain in the 2nd trimester: (A) Transventricular plane, showing anteriorly the frontal horns of the lateral ventricles, divided by the CSP, posteriorly the atria of the lateral ventricles, almost completely filled by the echogenic choroid plexuses; (B) transcerebellar plane showing the cerebellum and the cisterna magna; and (C) transthalamic plane showing the CSP, the thalami, and the hippocampal gyri

Figs 2A and B: Sagittal planes: (A) Midsagittal plane showing the CC located above the CSP and cavum vergae, the cerebellar vermis, and the fourth ventricle; and (B) parasagittal plane showing the lateral ventricle with the choroid plexus inside

Figs 3A to D: Coronal planes: (A) Transfrontal plane showing the frontal horns, the uninterrupted interhemispheric fissure and the orbits; (B) transcaudate plane showing the frontal horns above the caudate nuclei, divided by the CSP located below the CC; (C) transthalamic plane showing the thalami in close opposition; and (D) transcerebellar plane showing the occipital horns of the lateral ventricles and the cerebellar hemispheres

tilting the transducer from the anterior to the posterior aspect of the fetal head:

The transfrontal plane shows the frontal horns, the uninterrupted interhemispheric fissure, and the orbits (Fig. 3A).

The transcaudate plane shows the frontal horns above the caudate nuclei, divided by the CSP located below the CC (Fig. 3B).

The transthalamic plane shows the thalami in close opposition (Fig. 3C).

The transcerebellar plane shows the occipital horns of the lateral ventricles and the cerebellar hemispheres (Fig. 3D).

The expanded neurosonogram may be complemented by the use of the three-dimensional US technique.^{4,5} A volume of the fetal brain can be stored and then evaluated using a multiplanar view mode, which allows the contemporary view of the axial, coronal, and sagittal planes intersecting in a dot (Fig. 4). Further modalities are the tomographic ultrasonic imaging, which shows multiple

Fig. 4: Three-dimensional (3D) multiplanar mode with the contemporary view of the axial, coronal, and sagittal planes intersecting in a dot

Fig. 5: Three-dimensional tomographic ultrasonic mode showing multiple parallel scans in the coronal plane

parallel scans in axial, coronal, and sagittal planes (Fig. 5) in a way similar to computed tomography or magnetic resonance imaging (MRI),⁶ and the omniview technique that allows to choose any plane in the acquired volume.

The sonographic evaluation of the fetal CNS includes the visualization of the spine in sagittal, coronal, and transverse planes.

The sagittal planes show the ossification centers of the vertebral bodies and posterior arches forming two parallel lines that converge in the sacrum (Fig. 6). When the fetus is prone, a true sagittal plane can be obtained passing through the unossified spinal process and showing the spinal cord and the conus medullaris (Fig. 7).

Fig. 6: Sagittal plane of the spine showing the ossification centers of the vertebral bodies and posterior arches forming two parallel lines that converge in the sacrum

Fig. 7: True sagittal plane passing through the unossified spinal process and showing the spinal cord and the conus medullaris

Figs 8A and B: Axial planes of the spine showing the three ossification centers of the body and the laminae surrounding the spinal canal: (A) cervical level; and (B) thoracic level

Fig. 9: Coronal plane passing through the laminae and showing the vertebral canal

Figs 10A to C: Three-dimensional visualization of the spine: (A) Surface mode; (B) X-ray mode; and (C) silhouette mode

The axial planes show the three ossification centers of the body and the laminae surrounding the spinal canal and whose appearance changes according to the level of the scan (Figs 8A and B).

The coronal plane passing through the laminae shows the vertebral canal (Fig. 9).

An impressive visualization of the spine can be obtained with three-dimensional sonography by using the X-ray modality (Figs 10A to C).

Thanks to the development of high-resolution new machines and to the wide diffusion of the 1st trimester combined screening of chromosomal abnormalities, the

number of fetal anomalies detected in the 1st trimester is increasing. Although, the CNS has a complex and progressive development until the 3rd trimester, some anomalies may be recognized even in the 1st trimester. This topic will be examined in another article of this issue. The CNS anomalies detectable in the 2nd and 3rd trimesters of pregnancy will be now discussed.

VENTRICULOMEGALY

Fetal cerebral ventriculomegaly (VM) is defined as an enlargement of the ventricles of the developing fetal brain.

Figs 11A and B: (A) Mild ventriculomegaly; and (B) severe ventriculomegaly

The term hydrocephalus is frequently used as synonym, but it should be limited only to cases with increased pressure of cerebrospinal fluid (CSF) and usually increased head circumference.

The mechanisms producing VM can be different. It may be the consequence of an obstruction to flow or a hyperproduction of CSF. The obstruction may be internal or external to the ventricular cavities. Nonobstructive forms of VM may be secondary to hyperproduction (i.e., choroid plexus papilloma) or abnormal reabsorption of CSF. Ventriculomegaly may also be secondary to anomalies of the periventricular brain structures, which may be malformative (i.e., CC agenesis, neuronal migration, and proliferation disorders) or destructive lesions (tumors, vascular anomalies). In conclusion, VM is the sign common to different diseases.⁷

Ultrasound Diagnosis of Fetal VM

Measurement of the size of the fetal cerebral lateral ventricles is recommended as part of the fetal scan routinely performed during the 2nd trimester to screen for fetal anomalies. The measurement is done on the transventricular plane at the level of the atria of the lateral ventricles filled by the echogenic choroid plexuses. The calipers are positioned at the internal margin of the medial and lateral wall of the atria. An atrial width of less than 10 mm is considered normal. Ventriculomegaly is diagnosed when the width of one or both lateral ventricles, measured according to the criteria described so far, is ≥ 10 mm. Measurements between 10 and 14,9 mm constitute borderline VM, which can be divided in two subgroup: mild (10–12 mm) and moderate (12,1–14,9 mm) 15 mm constitute severe VM (Figs 11A and B).

Ventriculomegaly can be bilateral or unilateral. Usually in the US examinations, only the lateral ventricle distal to the transducer is measured since the proximal one is obscured by reverberation artifacts. Efforts should

be made in order to visualize both ventricles and recognize unilateral and bilateral VM; a useful scanning plane is the coronal on the posterior horns on the lateral ventricles (Fig. 12).

When a cerebral VM is recognized, it becomes important to rule out for associated abnormalities, chromosomopathies, and infectious diseases and to recognize the cause of the ventricular dilatation, since the prognosis and the parental counseling mainly depend on these factors.

Ventriculomegaly and Structural Abnormalities

Ventriculomegaly may be associated with neural and extraneural anomalies. Malformations are more often found in cases of severe VM; 60% of association has been reported, the most common ones being agenesis of corpus callosum (ACC) and spina bifida. Non-CNS malformations account for almost one-third of detected anomalies.⁸ The rate of association of structural abnormalities with mild VM varies widely from 10 to 76%, with an average value of 41.4%.⁹ Considering the high percentage of association with neural and extraneural abnormalities, a

Fig. 12: Coronal view on the posterior horns on the lateral ventricles showing unilateral VM

careful ultrasonic examination of the fetus with VM must be performed. Several brain abnormalities can be easily recognized by a detailed neurosonogram. The midsagittal view of the brain is a useful scanning plane, allowing the simultaneous visualization of two relevant landmarks of the brain, namely the CC and the cerebellar vermis. Looking at these landmarks, it is possible to recognize the most common causes of fetal VM: aqueductal stenosis, ACC, Chiari II malformation, and Dandy-Walker malformation.¹⁰ In aqueductal stenosis, the VM is isolated and in the midsagittal view CC and cerebellar vermis are normal (Fig. 13). In ACC, it is possible to demonstrate on the sagittal view the absence of the commissural fibers (Figs 14A and B). In Chiari II malformation the typical funneling of the posterior fossa may be seen (Figs 15A and B).

In Dandy-Walker malformation, the midsagittal view shows the upward rotated hypoplastic vermis, the cystic dilatation of the 4th ventricle, and the high insertion of the tentorium (Figs 16A and B). However, the list of brain anomalies which can be associated to VM is long: cysts, extra-ventricular tumors, choroid plexus papilloma, neuronal migration and proliferation disorders, vascular malformations, and hemorrhage. Some of these anomalies may have a late appearance during the 3rd trimester or may be so subtle to be missed by US.

In order to improve the diagnostic accuracy in recognizing associated anomalies, the use of MRI has been advocated. The brain pathologies associated with VM which could be missed by US and could be recognized by MRI are mainly represented by neuronal migration

Fig. 13: Aqueductal stenosis: The 3rd and lateral ventricles are dilated and the midsagittal view shows normal CC and cerebellar vermis

Figs 14A and B: Ventriculomegaly and ACC: The midsagittal view shows the absence of the commissural fibers

Figs 15A and B: Ventriculomegaly and Chiari II malformation: The typical funneling of the posterior fossa may be seen

Figs 16A and B: Ventriculomegaly and Dandy-Walker malformation: The midsagittal view shows the upward rotated hypoplastic vermis, the cystic dilatation of the 4th ventricle, and the high insertion of the tentorium

disorders, delayed sulcation and gyration, heterotopias, and intraparenchymal hemorrhage.¹⁰⁻¹² Since most of these pathologies develop late in pregnancy, the appropriate time to perform MRI is in the late 2nd or 3rd trimester.

Ventriculomegaly and Chromosomal Abnormalities

The incidence of chromosomal abnormalities is high (>15%) in both borderline and severe VM when a structural anomaly is associated. In cases of isolated VM, on the contrary, the association is relatively low. The incidence of abnormal karyotype in fetuses with isolated borderline VM varies widely in different studies with an average value of 2.7%.^{9,11,12}

Ventriculomegaly and Fetal Infections

Fetal infections, mainly toxoplasmosis and cytomegalovirus (CMV), may cause VM usually as a consequence of gliosis of the white matter surrounding the aqueduct and subsequent obliteration. Infections are more frequently found in cases of severe VM which develop in late pregnancy. The rate of infections in severe VM is 10 to 20%, while in borderline VM it is 1 to 5%.^{9,11,12}

Outcome of Fetal Ventriculomegaly

The outcome of fetuses with VM associated with neural or extraneural malformations and/or aneuploidies depends on the severity of the associated anomaly. In these cases, counseling the parents will be relatively simple, even though there are some associated anomalies which can carry an extremely variable prognosis, such as ACC. On the contrary, counseling is difficult in case of isolated VM. Studies on the long-term outcome of fetuses with VM (both severe and mild) are limited: Most of them are retrospective studies with different modalities of follow-up. The prognosis is worse in cases of isolated severe VM. The neurological outcome of fetuses with prenatal diagnosis of isolated borderline VM varies widely in different studies with an average value of neurological outcome of 11%.^{9,11,12} The explanation for the wide variation of the results reported by different authors is that different protocols are used to assess postnatal neurological development.

A factor that can significantly influence the prognosis is the progression of the VM in the ongoing pregnancy. In 15.7% of the cases, the VM progresses and these are the cases where the prognosis is worse.

DISORDERS OF VENTRAL INDUCTION

The process of ventral induction that leads to the development of the prosencephalon consists of three sequential events that are strictly connected: Formation, cleavage, and midline development. An impaired cleavage of prosencephalon produces holoprosencephaly (HPE); an abnormal prosencephalic midline development causes septo-optic dysplasia (SOD) and ACC.¹³

Holoprosencephaly

The term holoprosencephaly refers to a variety of congenital malformations of the CNS deriving from a failed or incomplete separation of the prosencephalon into two telencephalic vesicles, usually associated with facial anomalies, such as ciclopia (fused orbits with arinia and frontal proboscis), ethmocephaly (hypotelorism with arinia and proboscis), cebocephaly (hypotelorism and single nostril), and facial cleft. It is frequently associated with chromosomal abnormalities, mainly trisomies 13 and 18¹⁴ and it occurs in 1 per 10,000 to 15,000 live births. The incidence is even higher if abortions are taken into account (1:250).

According to the severity of the defect, three forms of HPE are described: Alobar, semilobar, and lobar. The alobar variety is characterized by the absence of interhemispheric fissure with a single ventricular cavity and thin layer of the cerebral cortex, fused thalami, and absence of 3rd ventricle; in the semilobar variety, a single ventricular cavity is present, while posteriorly the cerebral hemispheres are partially divided and surrounded by a layer of the cerebral cortex more represented than the previous form; in the lobar form, the interhemispheric fissure is normally developed with a partial fusion at the level of the frontal horns of the lateral ventricles and gyrus cinguli, with absence of CSP.¹⁵ However, there are no precise

boundaries among the three variants, and intermediate forms may be found. One variant is the middle interhemispheric HPE that mainly affects the dorsal forebrain.¹⁶

The prenatal sonographic diagnosis of HPE is generally easy in the alobar and semilobar varieties, whereas it is extremely difficult in the lobar form. In the alobar HPE, the fetal skull is occupied by a single ventricular cavity widely communicating with a posterior cystic structure named dorsal sac. The residual cerebral tissue is compressed upward and anteriorly and assumes a typical "boomerang" or "horseshoe" shape. Further, typical features are the absence of interhemispheric structures and the fused thalami (Fig. 17). These sonographic features are so relevant that they can be recognized even in the 1st trimester. An accurate evaluation of the fetal face allows the recognition of the associated facial abnormalities (Fig. 18).

In the semilobar variety, a single ventricular cavity is visible anteriorly, communicating posteriorly with rudimentary occipital horns.

The prenatal diagnosis of the lobar form is difficult since the fusion of the ventricular cavities is limited to the frontal horns. In the coronal section the fused frontal horns show a typical squared and flat roof (Fig. 19).

In cases of HPE, an accurate evaluation of the fetal face must be done. The facial anomalies include cyclopia, arhinia with or without proboscis, hypotelorism, median cleft lip, and palate. The prognosis of alobar HPE is fatal: most fetuses die *in utero* or in the early neonatal period. The semilobar variety produces severe neurologic dysfunctions, such as generalized hypotonia, seizures, cranial nerve involvement, and mental retardation. Mental retardation of variable severity occurs in the lobar form, but there are cases of infants who do not develop neurologic handicap.

Fig. 17: Alobar holoprosencephaly: The fetal skull is occupied by a single ventricular cavity, the interhemispheric structures are absent and the thalami fused

Figs 18: Cyclopia (arrows) and proboscis (P) associated with alobar holoprosencephaly

Fig. 19: Lobar holoprosencephaly: The fusion of the ventricular cavities is limited to the frontal horns: In the coronal section the fused frontal horns show a typical squared and flat roof

Fig. 20: Septo-optic dysplasia: The anterior coronal plane shows the two frontal horns fused as a consequence of the absent septum pellucidum. The normal presence of the CC and the fornix allows the differential diagnosis from lobar HPE

Septo-optic Dysplasia (SOD)

The term septo-optic dysplasia refers to the heterogeneous conditions characterized by agenesis of the septum pellucidum, optic nerve hypoplasia, and pituitary hypoplasia. In some cases, schizencephaly, ACC, and cortical malformations are associated (SOD-plus).

The sonographic diagnosis is possible on the anterior coronal plane passing through the frontal horns of the lateral ventricles. The two frontal horns are fused as a consequence of the absent septum pellucidum.¹⁷ The normal presence of CC and the fornix allows the differential diagnosis from lobar HPE (Fig. 20). The differentiation of SOD from isolated agenesis of the septum pellucidum is extremely difficult: an attempt to recognize the optic nerve hypoplasia could be tried by using MRI in the 3rd trimester; the pituitary hypoplasia could be evaluated by fetal blood assays of growth hormone (GH), adrenocorticotrophic hormone (ACTH), and prolactin (PRL). However, the optic nerve hypoplasia and the hormonal disorders may develop very late in pregnancy or even after delivery.

The clinical manifestations of SOD include visual disturbances (blindness in the most severe forms) and signs of hypothalamic-pituitary insufficiency (growth failure, diabetes insipidus).

Agenesis of Corpus Callosum

The CC is the major interhemispheric commissure made of bundles of white matter extending from one hemisphere to the other. A callosal plate is already present at 12 to 14 weeks of gestation, but the development of the CC is complete at around 20 weeks. The CC is composed of four parts that, from the anterior to the posterior aspect, are: Rostrum, genu, body, and splenium. The development of the CC starts from the genu and progresses posteriorly

to the body and splenium. The rostrum is considered the last part to develop, even though some authors suggest that it is already present at 15 weeks of gestation. The abnormal development of the CC may lead to its complete or partial agenesis. In case of partial agenesis, since the development progress from front to back, the genu is present and the posterior portion of the body and the splenium are absent or hypoplastic.

The etiology is heterogeneous, but genetic factors are predominant. Over 50 genetic syndromes are known that may present partial or total ACC.

The sonographic diagnosis of ACC may be easily missed since the CC is not depicted in the axial planes used during the screening examination made in the 2nd trimester. However, using the axial planes the diagnosis can be suspected using the following indirect signs (Figs 21A to C)^{18,19}:

- The CSP is absent in complete ACC.
- The lateral ventricles have a teardrop appearance (colpocephaly) due to the enlargement of the trigones and occipital horns.
- The interhemispheric fissure is enlarged and the bodies of the lateral ventricles are parallel and shifted laterally by the white fibers failing to cross the midline.
- In 50% of the cases the 3rd ventricle is slightly enlarged and shifted upward between the lateral ventricles and sometimes may communicate with an interhemispheric cyst.

The definitive diagnosis relies on the demonstration of the absence of the complex formed by the CC and CSP. This sign can be achieved by the sagittal and coronal sections. The midsagittal section will demonstrate the complete or partial absence of the CC (Figs 22A and B): in cases of partial agenesis the CSP is present and only the splenium of the CC is missing.²⁰ In the 3rd trimester the gyri and sulci of the medial hemispheric surface show

Figs 21A to C: Indirect signs of complete ACC. The CSP is absent and the lateral ventricles have a teardrop appearance (colpocephaly) due to the enlargement of the trigones and occipital horns (A); the interhemispheric fissure is enlarged and the bodies of the lateral ventricles are parallel and shifted laterally by the white fibers failing to cross the midline (B); the 3rd ventricle is slightly enlarged and shifted upward between the lateral ventricles and sometimes may communicate with an interhemispheric cyst (C).

Figs 22A and B: Midsagittal plane in case of complete (A) and partial (B) ACC. In the complete form CC is absent. In the partial agenesis, the CSP is present and only the splenium of the CC is missing

an atypical radiate appearance, due to the absence of the gyrus cinguli. With the use of color-Doppler, the absence of the semicircular loop normally formed by the pericallosal artery can be noticed. The coronal section at the level of the frontal horns will show their typical “bull-shape” appearance due to the medial compression by the white fibers that fail to cross the hemispheres (bundles of Probst) (Fig. 23).

The prognosis of ACC mainly depends on the presence of associated anomalies. Agenesis of CC is associated with other CNS anomalies (such as Dandy-Walker malformation, gyral anomalies, neuronal heterotopia) in up to 80% of the cases. Some of these anomalies may be diagnosed only in the 3rd trimester with the use of MRI or even after delivery. The association with extra CNS malformation (cardiac, skeletal, and gastrointestinal anomalies) is up to 60%. Furthermore, it may be part of several congenital syndromes and metabolic diseases. For these reasons, it is not possible to draw prognostic conclusion at 20 to 22 weeks even when the ACC seems to be isolated. Finally, even if isolated complete or partial ACC is confirmed postnatally, a neurodevelopmental delay may be present in 15 to 36% of the cases.²⁰⁻²³

Fig. 23: Complete ACC: The coronal section at the level of the frontal horns shows their typical “bull-shape” appearance (arrows); the 3rd ventricle is dilated and communicates with an interhemispheric cyst

Neuronal Proliferation, Migration, and Differentiation Disorders

This group includes all events that inhibit or alter the neuronal and glial proliferation, neuronal migration, or subsequent cortical organization leading to the abnormal

Fig. 24: Microcephaly: Abnormal fetal profile, with a flat and low frontal pole as a consequence of the failure of brain development mainly interesting the forebrain

Fig. 25: Unilateral megalencephaly: An asymmetry between the two hemispheres with shifted midline structures and unilateral VM may be seen

development of the brain cortex. Since this is one of the last phases of the intrauterine development of the brain, the prenatal sonographic diagnosis is usually late.

Microcephaly is the most severe form of the neuronal proliferation disorders. It is the result of a reduced glial and neuronal proliferation and increased apoptosis. The etiology of this pathology is heterogeneous: Both genetic and environmental origins (infections, toxic agents, drugs) are known. The neurologic outcome depends on the etiology and the severity of the defect.²⁴

The prenatal sonographic diagnosis is usually late, since it relies on biometric criteria which become evident in the late 2nd and 3rd trimesters.²⁵ The diagnosis is based on the recognition of a small head circumference <3 SD for the gestational age; especially when gestational age is not certainly known, an additional diagnostic aid is the comparison of the head circumference to the abdominal circumference and to the femur length. The head circumference/abdominal circumference ratio >3 SD and a femur length/head circumference ratio <3 SD for the gestational age are suspicious findings of microcephaly. Since the failure of brain development mainly interests the forebrain, an abnormal fetal profile, with a flat and low frontal pole is a further sonographic sign of microcephaly²⁶ (Fig. 24).

Macrocephaly is characterized by a large head with no evidence of hydrocephaly or intracranial masses. The clinical significance of this condition is unclear, since large brain has been reported both in normal and mentally retarded cases.

Unilateral megalencephaly is an extremely rare condition characterized by an abnormal growth of one cerebral hemisphere in comparison to the opposite one. In this case, US shows an asymmetry between the two hemispheres with shifted midline structures and unilateral VM²⁷ (Fig. 25).

The term lissencephaly refers to a smooth outer brain surface, characterized by a paucity of gyral and sulcal development. It is a cortical malformation characterized by the reduction (pachygyria) or absence (agyria) of the cerebral gyri and includes subcortical band heterotopias²⁸; since their development occurs in the 3rd trimester, the prenatal diagnosis is possible only in late pregnancy. Based on brain pathology, lissencephaly is classified into three groups:

1. Classic lissencephaly (agyria): Cerebral cortex is composed of four layers, instead of the traditional six, as a result of incomplete migration of neurons.
2. Cobblestone complex: Irregular cerebral cortex with distorted cytoarchitecture, as a result of neuroglial overmigration into the arachnoid space.
3. Subcortical band heterotopias: Arrest of migration of normal neurons along the radial glial path between the ependymal of the lateral ventricle and the cortex.

The sonographic suspicion may arise when the opercula fail to grow and cover the insula (Fig. 26) or when

Fig. 26: Microlissencephaly: The hemispheres are small, the brain surface is smooth, and mild VM is present

Fig. 27: Schizencephaly: A part of the brain cortex is absent and the ventricular cavity widely communicates with the arachnoid space

Fig. 28: Brain teratoma appearing as complex mass with solid and cystic areas and with irregular borders

the parieto-occipital, sylvian, and calcarine fissure are not yet developed at 22 to 23 weeks.²⁹ It often presents with isolated mild VM at the mid-trimester scan that suggests a follow-up US examination at 24 to 25 weeks. This diagnosis, however, is not easy and can be suspected only when associated intracranial anomalies are present or a familiar history is referred.³⁰ The prognosis is poor and characterized by severe mental retardation, hypotonia, convulsions, and death during the first 5 years of life. The prognosis is less severe in cases of heterotopia.

In schizencephaly, a part of the brain cortex is absent and the ventricular cavity widely communicates with the arachnoid space (Fig. 27). It can be unilateral or bilateral, symmetric or asymmetric. Two types of schizencephaly are known: The first one with a very thin cleft (closed lip schizencephaly), and the second one with a cleft filled with CSF and often associated with VM (open lip schizencephaly). The latter form is often associated with SOD. Only the open lip schizencephaly has been diagnosed *in utero*.^{31,32} In cases of open lip schizencephaly, the prognosis is poor and it is generally associated with seizures and severe mental retardation.

Occupying Space Lesions

This group includes lesions of different nature (tumors, vascular lesions, and cysts) which distort and/or compress the brain structures.

Brain Tumors

Congenital brain tumors are extremely rare events. Their location, biologic behavior, and histologic types are different. They are more frequently located in the supratentorial space. The most common type of congenital brain tumor is teratoma.³³

The sonographic patterns of fetal brain tumors change according to the histologic type.^{34,35} Teratoma is usually located in the supratentorial space and appears as complex mass with solid and cystic areas and with irregular borders (Fig. 28). The tumor may undergo quick growth and reach huge size causing macrocrania, distortion of the brain, and sometimes also of the face anatomy. It may present calcifications and frequently a rich vascularization at color Doppler. Sometimes teratomas may undergo cystic degeneration as a consequence of intratumoral hemorrhage and infarction, thus assuming the appearance of a multicystic lesion. Primitive neuroectodermic tumors, astrocytomas, and craniopharyngiomas show sonographic patterns similar to teratomas. Lipomas are mainly located in the area of CC and are hyperechoic with a typical curvilinear shape in the sagittal section. Choroid plexus papilloma appears as a hyperechoic mass inside a dilated lateral ventricle; the VM is secondary to the hyperproduction of CSF.

Huge brain tumors are responsible for macrocrania. Ventriculomegaly may develop as a consequence of the obstruction of liquor circulation. Polyhydramnios is frequently associated. The prognosis of congenital brain tumor is extremely poor, particularly in cases of teratomas, in which much of the brain may be replaced by the tumor mass. The survival rate at 1 year of life is only 7% and falls to 3% in cases diagnosed before 30 weeks of gestation.

Brain Cysts

According to their location brain cysts may be differentiated into two main subgroups: Extra-axial cysts and periventricular cysts.

Extra-axial cysts

These cysts are also known as arachnoid cysts. They are benign cystic collection of CSF in the space between

Fig. 29: Arachnoid cyst appearing as thin-walled unilocular cystic mass compressing the brain parenchyma

the pia mater and the inner layer of the arachnoid (sub-arachnoid) or between the two layers of the arachnoid (intra-arachnoid). They are usually sporadic and isolated lesions, representing 1% of all neonatal nontraumatic intracranial masses. They may be primitive or secondary to adhesions by infections, hemorrhage, and trauma. As regards to their location, they are mainly supratentorial: 50% of the cases are located in the middle fossa, 5 to 10% in the suprasellar cistern, 5 to 10% in the quadrigeminal cistern, 5% along the convexities, and 5 to 10% in the posterior fossa.³⁶

In 55% of the cases, the diagnosis is made between 20 and 30 weeks of gestation; in 45% after 30 weeks. They appear as thin-walled uni- or multilocular cystic masses of variable size located in different parts of the brain (Fig. 29). There is no communication with the ventricular cavities. Ventriculomegaly may be associated as a consequence of obstruction to the liquor circulation mainly at the level of the aqueduct of Sylvius. However, there is no correlation between the cyst size and VM. Huge cysts cause displacement but not destruction of the surrounding brain structures. The midsagittal view of the fetal brain is useful to correctly locate the small

interhemispheric cysts, thus allowing to differentiate quadrigeminal cistern cysts, cavum veli interpositi cysts, and suprasellar cysts^{37,38} (Figs 30A to C). The differential diagnosis includes: porencephalic cysts and schizencephaly. Porencephalic cysts may be primitive or secondary to infections or vascular accidents; they are usually located inside the brain parenchyma and may communicate with the ventricular cavities (Fig. 31). Schizencephaly may be a sign of neuronal migration disorder or may be secondary to a vascular accident; ultrasonically, there is a lack of brain tissue between the lateral ventricle and the subarachnoid space (Fig. 27).

The natural history of arachnoid cysts is variable: some of them may increase in size during gestation; others decrease or even disappear *in utero* or after delivery. Resolution *in utero* is rare (3.7%), and it is more frequent after delivery (23.9%).

The postnatal outcome is independent of the size and location of the cyst, but mainly depends on the integrity of the surrounding cerebral structures. In most cases, however, the prognosis is good and surgery is needed only in symptomatic cases or in cases of progressive growth of the cysts.³⁹

Periventricular Cysts

Also defined as subependymal, these cysts usually appear after 25 to 26 weeks of gestation. They may be single or multiple, uni- or bilateral, usually of small size (few millimeters) and completely anechoic (Fig. 32). These cysts or pseudocysts are usually located at the level of the germinal matrix below the frontal horns of the lateral ventricles. They may be the natural evolution of a small subependymal hemorrhage, the consequence of a hypoxic-ischemic event, or may be the result of post-infectious germinolysis caused by neurotropic viruses (CMV, rubovirus). They may also be present in cases of genetic disorders, such as Zellweger syndrome. In a high percentage of cases, however, they have no clinical consequence and may regress spontaneously *in utero* or after delivery.^{40,41} The differential diagnosis is to be

Figs 30A to C: Midsagittal view of the fetal brain in different types of interhemispheric cysts: (A) Quadrigeminal cistern cysts; (B) cavum veli interpositi cyst; and (C) suprasellar cyst

Fig. 31: Porencephalic cyst: It is located inside the brain parenchyma and communicates with the ventricular cavities

Fig. 32: Subependymal cysts located at the level of the germinal matrix below the frontal horns of the lateral ventricles

Fig. 33: Multiple cystic lesion located above the frontal horns in case of cystic periventricular leukomalacia

Fig. 34: Vein of Galen aneurysmal malformation: It appears as a supratentorial tubular structure located in the midline, showing a typical turbulent flow at color Doppler

made with the cystic periventricular leukomalacia. In this case the cystic lesions are located above the frontal horns (Fig. 33). These lesions are typical of the premature neonate and develop as a consequence of necrosis of the matter due to a hypoxic-ischemic event. Sometimes, they develop *in utero* and in this case, the prognosis is extremely poor, since cystic periventricular leukomalacia is considered the most predictive sign of cerebral palsy.

Vein of Galen Aneurysmal Malformation (VGAM)

This is a complex arteriovenous malformation, characterized by multiple vascular communications between the vein of Galen system and cerebral arteries (carotid or basilar arteries). The prenatal diagnosis is usually late, since the vascular lesion shows a progressive increase in size with the progression of pregnancy. It appears as a supratentorial tubular anechoic structure located in the midline above the cerebellum.⁴² The color-Doppler shows

a typical turbulent flow (Fig. 34). The possible complications of such an abnormal flow are:

- Cardiomegaly with cardiac failure, hepatomegaly, hydrops, and polyhydramnios as a consequence of the left/right shunt.
- Ventriculomegaly secondary to venous hypertension or compression of the ventricular system.
- Cerebral atrophy secondary to decreased blood flow to the brain parenchyma.

In the presence of such complications, the prognosis is poor. In isolated cases a postnatal embolization may be planned with good results.

Posterior Fossa Abnormalities

Posterior fossa abnormalities refer to a variety of CNS anomalies, characterized by an abnormal configuration of the cerebellum and/or the cisterna magna. Different classifications exist of the posterior fossa malformations

according to their embryological, etiological, or morphological patterns. From the imaging point of view, the most simple and useful classification is the morphological one, including the following categories^{43,44}:

- Anomalies characterized by the presence of a retrocerebellar fluid collection (or “cystic lesions”): Dandy-Walker malformation, cerebellar vermis hypoplasia, Blake’s pouch cyst, mega cisterna magna, arachnoid cyst.
- Anomalies characterized by abnormal morphology of the cerebellum with normal retrocerebellar fluid (cerebellar hypoplasia, rhombencephalosynapsis, focal anomalies, or acquired insults).
- Anomalies characterized by a small and crowded posterior fossa (Chiari II malformation).

Dandy-Walker malformation (DWM) is characterized by a total or partial agenesis of the cerebellar vermis that appears upward rotated with cystic dilatation of the 4th ventricle widely communicating with the cisterna magna.^{45,46} The tentorium is elevated and VM is frequently associated (Figs 35A and B). The risk of chromosomal anomalies is high, with up to 35% of cases being

associated with aneuploidy, mainly trisomy 18 and 13. The prognosis of fetuses affected by DWM is poor, mainly if it is associated with VM or other CNS anomalies; in these, cases the overall mortality rate is over 60% and most survivors have a low IQ.

In vermian hypoplasia, the cerebellar vermis is mildly hypoplastic, mainly in its inferior portion, and is slightly rotated upward. The size of the posterior fossa is normal and the tentorium is normally inserted^{47,48} (Figs 36A and B). The risk of chromosomal anomalies is high. The prognosis is variable according to the genetic and embryological condition causing the disease. In truly isolated cases, a normal development may be expected in up to 60% of the cases.

In Blake pouch cyst (BPC), the cerebellar vermis is normal both in morphology and size, but it is slightly rotated upward by a finger-like protrusion of the 4th ventricle secondary to failure of formation of foramen of Magendie and Luschka. The size of the posterior fossa, the tentorial insertion, and the cisterna magna are normal (Figs 37A and B). The prognosis is usually good with possible spontaneous resolution in late pregnancy. In some progressing cases, VM may develop in postnatal age.^{49,50}

Figs 35A and B: Dandy-Walker malformation: The axial plane (A) shows a wide cyst in the posterior fossa; the midsagittal plane (B) shows the hypoplastic upward rotated cerebellar vermis, the cystic dilatation of the 4th ventricle widely communicating with the cisterna magna and the elevated tentorium

Figs 36A and B: Vermian hypoplasia: The axial plane: (A) A small cyst between the cerebellar hemispheres; the midsagittal plane; and (B) a mildly hypoplastic and slightly upward rotated cerebellar vermis; the size of the posterior fossa is normal and the tentorium is normally inserted

Figs 37A and B: Blake pouch cyst: The axial plane: (A) A small cyst between the cerebellar hemispheres; the midsagittal plane; and (B) a normal vermis that is slightly rotated upward by a finger-like protrusion of the 4th ventricle secondary to failure of formation of foramen of Magendie and Luschka; the size of the posterior fossa, the tentorial insertion, and the cisterna magna are normal

Figs 38A and B: (A) In mega-cisterna magna there is only an enlarged cisterna magna (more than 10 mm width); and (B) no apparent vermian defect or rotation

In mega-cisterna magna, there is only an enlarged cisterna magna (more than 10 mm width) without VM and no apparent vermian defect or rotation (Figs 38A and B). The prognosis is usually good in isolated cases.⁵¹

Arachnoid cysts appear as infra-tentorial cystic lesions producing compression and displacement of a normal cerebellum (Fig. 39). The prognosis is usually good.

It must be stressed that an uncorrected axial transcerebellar scan may offer a wrong impression of vermian defect even in normal fetuses if the ultrasonic beam passes through the vallecula of Reil, which is the anatomic space where the inferior aspect of the cerebellar hemispheres meets the cisterna magna. In this case, the sagittal scan allows to recognize the normality of cerebellar vermis.

Cerebellar hypoplasia and rhombencephalosynapsis are two anomalies characterized by abnormal cerebellum with normal retrocerebellar fluid. In the former, the cerebellum is smaller than normal (both hemispheres and vermis) (Figs 40A and B); in the latter, the cerebellum is smaller and dysmorphic as a consequence of the failed development of the vermis with fused cerebellar hemispheres^{52,53} (Fig. 41). In both cases, the prognosis is poor.

Fig. 39: Posterior fossa arachnoid cyst appears as an infra-tentorial cystic lesion producing compression and displacement of a normal cerebellum

Chiari II malformation is characterized by a small and crowded posterior fossa. It is the consequence of an open spina bifida with tethered cord producing a downward displacement of the hindbrain. The axial transcerebellar plane shows the typical banana shape of the cerebellum

Figs 40A and B: Cerebellar hypoplasia: The cerebellum is smaller than normal (both hemispheres and vermis)

Fig. 41: Rhombencephalosynapsis: The cerebellum is smaller and dysmorphic as a consequence of the failed development of the vermis with fused cerebellar hemispheres

Fig. 42: Anencephaly at 12 weeks of gestation

and the cisterna magna is effaced. The sagittal plane shows the funneling shape of the posterior fossa with the effaced cisterna magna⁵⁴ (Fig. 15).

Neural Tube Defects

The term neural tube defects (NTD) refers to a variety of congenital malformations secondary to a failed closure of the neural tube in the earliest stages of CNS development, during gastrulation (2nd–3rd week), primary neurulation (3rd–4th week), and secondary neurulation (5th–6th week). According to the level and severity of the defect, different pathologies may develop, ranging from very severe forms incompatible with the postnatal life, such as anencephaly, to minor forms amenable of surgical correction, such as small meningoceles.

Anencephaly is a very severe anomaly of the CNS characterized by the absence of the cranial vault with protrusion of cerebrovascular tissue in the amniotic fluid. The sonographic diagnosis, based on the lack of visualization of the fetal skull, is very easy and can be done even in the 1st trimester of pregnancy at 11–12 weeks (Fig. 42). At this early stage the cerebral hemisphere surrounded by a thin membrane in direct contact with the amniotic fluid

may still be visible (acrania) or redundant brain tissue may protrude from the absent cranium (exencephaly).⁵⁵ Anencephaly is incompatible with postnatal life and termination of pregnancy may be offered to the parents.

Iniencephaly is an extremely rare malformation characterized by a bony defect at the occipital level (“inion”) associated to cervical dysraphism. The typical sonographic feature is a constant and exaggerated hyperextension of the fetal head.

Cephalocele is a malformation characterized by the protrusion through a bony defect of the calvarium, of meninges alone (“meningocele”), or associated brain tissue (“encephalocele”). In most cases, the defect is located on the midline, mainly at the level of the occipital bone and can be associated in 7 to 15% of the cases with spina bifida. Location different from the midline are consequence of skull amputation secondary to amniotic band.⁵⁶ Cephalocele should be caused by a lack of fusion of the neural tube at specific sites, even if some authors have postulated postneurulation events with anomaly of the mesenchymal induction of brain tissue. Cephalocele may sometimes be part of complex syndromes, such as the Meckel syndrome, characterized by polycystic kidneys, polydactyly, and cephalocele. The sonographic diagnosis

Figs 43A and B: Cephalocele appearing as complex mass protruding from a bony defect located at the occiput

is based on the recognition of a cystic or complex mass protruding from a bony defect, usually located at the occiput (Figs 43A and B), rarely on the frontal or nasopharyngeal regions. The size of the mass varies widely, from very small to giant cephaloceles, with secondary microcephaly or hydrocephaly. An asymmetric evidence of cephalocele is possible in the presence of amniotic band. The prognosis of a fetus affected by cephalocele mainly depends on the presence of brain tissue into the herniated sac, the volume of the defect, the association of microcephaly or hydrocephaly, or other noncerebral anomalies.⁵⁷

Spina bifida includes a spectrum of anomalies of different severity characterized by spinal dysraphism, secondary to failed closure of the caudal neural tube during neurulation. The defect is almost constantly posterior and is divided into two groups: Closed and open spina bifida. In the former case, the defect is small and covered by skin and is usually asymptomatic; in the open spina bifida the defect is on both the vertebra and the covering skin, with exposure of the neural tissue. The defect may be covered by a meningeal membrane containing only CSF (meningocele) or fluid and neural tissue (meningomyelocele).

Most cases of open spina bifida are associated with the Chiari II malformation.

Sonographic diagnosis is based on direct and indirect signs. The significant increase in the detection rate of this anomaly is related mainly to indirect signs, a sensitive indicator of this malformation.

Direct Sign: On axial scan the diagnosis is based on the recognition of the failed posterior fusion of the ossification centers of the laminae, producing the typical “U”-shaped appearance of the vertebra (Fig. 44A). The presence of a spina bifida may also be suspected in the coronal section passing through the laminae, which shows a typical enlargement of the spinal canal at the level of the vertebral defect with the disappearance of typical track image (Fig. 44B). An antero-posterior sagittal section is not useful, since in this case the shadow produced by the vertebral bodies may obscure the posterior defect. It is important to obtain a postero-anterior sagittal section in order to evaluate the size and extent of the defect. The presence of a meningocele or meningomyelocele facilitates the diagnosis by the recognition of a cystic or complex mass of different size located on the posterior aspect of the spine⁵⁸ (Fig. 45).

Figs 44A and B: Open spina bifida: On the axial scan (A) the failed posterior fusion of the ossification centers produces a typical “U”-shaped appearance of the vertebra; the coronal section passing through the laminae (B) shows a typical enlargement of the spinal canal at the level of the vertebral defect with the disappearance of typical track image

Fig. 45: Meningocele appearing as a cystic mass located on the posterior aspect of the spine

Figs 46A and B: Indirect signs of open spina bifida: (A) Hypoplastic posterior fossa with small or absent cisterna magna and dysmorphic cerebellum ("banana" sign) and deformity of the frontal pole of the skull ("lemon" sign); and (B) dilatation of the lateral ventricles

Indirect Sign: Since spina bifida is almost constantly associated with Chiari II malformation, the intracranial findings of this malformation can be looked for in the screening examination. These signs include⁵⁹ (Figs 46A and B):

- Hypoplastic posterior fossa with small or absent cisterna magna and dysmorphic cerebellum ("banana" sign).
- Deformity of the frontal pole of the skull ("lemon" sign).
- Dilatation of the lateral ventricles.

The small posterior fossa is the most sensitive sign, whereas the "lemon" sign is present in the 2nd trimester but disappears in the third one and the VM is not constantly associated.⁶⁰ The recognition of one of the above-mentioned signs is an indication to an accurate evaluation of the spine to look for a spinal defect. However, in screening procedures on normal population, small defects may be undiagnosed.

Recently, it has been reported that fetuses with open spina bifida are easily detectable by looking at the posterior fossa in the 1st trimester. At 11 to 14 weeks, the

4th ventricle appears as a fluid-filled translucent region (named intracranial translucency) with two echogenic horizontal borders, representing the posterior border of the brainstem anteriorly and the echogenic thin choroid plexus of the 4th ventricle posteriorly. The fluid of the future cisterna magna is readily identified between the choroid plexus and the occipital bone. In cases of spina bifida, the intracranial translucency is absent or smaller as an early manifestation of the Chiari II malformation.⁶¹

The prognosis of the fetuses affected by spina bifida depends on the entity and the level of the defect: The larger and the higher is the defect, the more severe is the neurological deficit.⁶² Location above L3 level are usually associated with severe walking impairment. The association with other anomalies, mainly hydrocephalus, is another important prognostic factor.

Recently, fetal surgery for closure of spina bifida has been suggested. This treatment performed before 26 weeks of gestation may preserve neurologic function, reverse the hindbrain herniation of the Chiari II

malformation, and obviate the need for postnatal placement of a ventriculoperitoneal shunt. However, it is associated with significant risks related to the uterine scar and premature birth.⁶³

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