Imaging the fetal central nervous system

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Abstract

The low prevalence of fetal central nervous system anomalies results in a restricted level of exposure and limited experience for most of the obstetricians involved in prenatal ultrasound. Sonographic guidelines for screening the fetal brain in a systematic way will probably increase the detection rate and enhance a correct referral to a tertiary care center, offering the patient a multidisciplinary approach of the condition.

This paper aims to elaborate on prenatal sonographic and magnetic resonance imaging (MRI) diagnosis and outcome of various central nervous system malformations. Detailed neurosonographic investigation has become available through high resolution vaginal ultrasound probes and the development of a variety of 3D ultrasound modalities e.g. ultrasound tomographic imaging. In addition, fetal MRI is particularly helpful in the detection of gyration and neurulation anomalies and disorders of the gray and white matter.

Key words: central nervous system, fetal imaging, prenatal MRI, brain malformation

Introduction

Cerebral malformations are encountered in about 1% of all births (Pinar et al., 1998). About 0.61% of children admitted to a pediatric clinic present with solitary or multiple central nervous system (CNS) malformations (Hadzagić-Catibusić et al., 2008). Nearly 10% of all congenital malformations in perinatal autopsy series are CNS anomalies, among which neural tube defects (45.5%), hydrocephaly (12.4%) and neuronal proliferation disorders (8.8%) are among the most frequently encountered (Pinar et al., 1998; Lancaster et al., 1981-1992). Frequently additional cerebral, extra-cerebral, syndromic and chromosomal malformations are associated (Weichtert et al., 2010). Still in about 60% of cases the etiology of cerebral malformation remains unknown.

The low prevalence of fetal central nervous system anomalies results in a limited possibility of training and therefore narrows the experience of most obstetricians. Sonographic guidelines for screening the fetal brain in a systematic way may increase the detection rate (Salomon et al., 2011). However, prenatal counseling regarding the prognosis of many of central nervous system anomalies remains difficult, because of the high rate of pregnancy terminations and the lack of long term follow-up studies for most of these conditions.

Suspicion of a CNS abnormality requires a multidisciplinary approach (Patel et al., 2008; Mighell et al., 2009). Maternal TORCH (toxoplasmosis, rubella, Cytomegalovirus, Herpes simplex) screening and amniocentesis for karyotyping and PCR (polymerase chain reaction), comparative genomic hybridization (CGH) arrays and eventually next generation sequencing and exclusion of viral infections may be recommended. Some patients may benefit from delivery, neonatal work-up and further surgical approach in a tertiary care centre, as e.g. the aneurism of the vene of Galen (Lasjaunias et al., 2006). Future neurodevelopmental follow-up of neonates with brain anomalies should be assessed by developmental neurologists and a team of co-workers.
When parents opt for termination of pregnancy, virtual autopsy with MRI and pathological examination should be part of the postmortem investigation (Brodlie et al., 2002). Confronted with the diagnosis of a congenital malformation, decisions are guided by the parents' personal background, family support, education, and culture. This process of framing takes time and may substantially differ individually (Bijma et al., 2005).

The scope of this paper is to elaborate on prenatal sonographic and MRI diagnosis and outcome of various CNS malformations, in particular those where significant progress has been made towards diagnosis, evaluation of prognosis, and possible treatment.

Development and sonoembryology of the fetal brain

Brain development consists of a continuum of events occurring at specific periods of time in gestation (Volpe, 2000). Extensive clinical research on brain development in the first trimester of pregnancy has become possible with the use of high frequency transvaginal ultrasound probes. Ventral induction by notochord-prechordal mesoderm induces the division of the prosencephalon into two lateral telencephalic vesicles and the diencephalon. This process is closely related to the development of the mid-facies (Volpe, 2000). The mesencephalon develops into the midbrain and the rhombencephalon further develops into the metencephalon and myelencephalon. These structures can be visualized in the human fetus from 6 weeks onward (Blaas et al., 2009). From 8 weeks onward, the choroid plexus in the lateral ventricles becomes visible. The falx cerebri appears at about 9 weeks. Over the next few weeks, the wall of the diencephalon thickens due to the development of the thalami. The insula appears as a shallow depression on the surface of the hemispheres and using color Doppler flow, the area of the developing corpus callosum (CC) can be identified on a mid-sagittal section (Blaas et al., 2009) at the end of the first trimester. The cerebellar hemispheres are clearly visible moving towards the midline.

At the end of the first trimester the third and fourth ventricle and the cistern magna are visible. In the second trimester the relative size of the lateral ventricles and choroid plexus decreases as the cerebral cortex develops progressively through neuronal migration, cerebellar hemispheres will fuse, the insula deepens and will be covered by the opercula. The CC becomes clearly visible at around 20 weeks of gestation (Loeser et al., 1968). Fetal cortical development had been studied by ultrasound from 18 weeks onwards, and correlates significantly with fetal brain MRI (Cohen-Sacher et al., 2006). The identification of major sulci, detectable by dedicated

**Fig. 1.** — The transthalamic and transcerebellar reference planes are used for structured analysis of the fetal brain in the second trimester.
neurosonography from 26 weeks onward (Cohen-Sacher et al., 2006) and measurement fissures depth may enhance the diagnosis of maturation disorders during pregnancy (Alonso et al., 2010).

Screening for brain anomalies during pregnancy

The three classical axial sections through the fetal head permit the evaluation of the fetal brain anatomy from the second trimester onward (Salomon et al., 2011). The transthalamic (Fig. 1) and the more cranial and parallel transventricular plane display the minimal requirements for basis mid trimester anatomical survey of the cerebrum (Salomon et al., 2011). The transcerebellar plane, obtained by rotating the probe posteriorly over 30 degrees, images the posterior fossa (Fig. 1). Systematic approach of these planes allows the direct evaluation of the lateral ventricles and the choroid plexus, the cavum septi pellucidi, the midline falx, the thalami, the cerebellum, and the cisterna magna.

Nevertheless, up to 20% of CNS related malformations may lead to a late termination of pregnancy (Barel et al., 2009), because of late and progressive development of the brain malformations, lack of follow-up of the patient or inadequate training of the sonographer.

Patients at increased risk should be referred to a level III centre for a dedicated neurosonogram. By means of transabdominal or transvaginal ultrasound, coronal, sagittal and parasagittal sections through the brain using high frequency probes enable detailed visualization of most cerebral and cerebellar structures (Cohen-Sacher et al., 2006; Alonso et al., 2010; Toi et al., 2004). Adding color Doppler flow imaging highlights the identification arterial perfusion and the venous drainage though the sinuses.

In addition, 3D-4D transabdominal or transvaginal ultrasound allows for fast and reliable acquisition of volumetric data sets of the fetal brain to be examined offline or send for second opinion. Simultaneous analysis in the three orthogonal planes facilitates the basic as well as the detailed structural evaluation of the brain (Monteagudo et al., 2009; Bornstein et al., 2010; Pilu et al., 2007; Correa et al., 2006; Viñals et al., 2007; Pilu et al., 2006), and is an excellent tool for teaching purposes. It allows the assessment of fetal brain sulci and gyri from 20 weeks onward (Rolo et al., 2011). Detailed analysis of the vermician development has been described (Zalel et al., 2009). Tomographic ultrasound imaging displays the fetal brain in a predefined number of slices at a fixed interval, and even early anatomy of the developing brain vesicles can be demonstrated (Hata et al., 2009).

### Table 1. — Clinical classification of central nervous system malformation in the fetus.

| Category                        |
|--------------------------------|
| isolated ventriculomegaly      |
| neural tube defects            |
| midline defects                |
| destructive lesions            |
| proliferation disorders        |
| vascular malformations         |
| tumors and cysts               |
| intracranial hemorrhage        |

### Table 2. — Classification of intraventricular hemorrhage

| Grade   | Description                                      |
|---------|--------------------------------------------------|
| I       | Germinial matrix bleeding                        |
| II      | Intraventricular, no hydrocephaly                |
| III     | Intraventricular, with ventricular dilatation    |
| IV      | Intraventricular, with parenchymal hemorrhage and hydrocephaly |

### Congenital malformations

Clinically, CNS malformations can be classified into several pathological groups (Table 2).

### Isolated mild ventriculomegaly

Isolated mild to moderate ventriculomegaly is defined as a lateral ventricle wider than 10 mm, but less than 15 mm. It is the most common non-specific abnormality of the CNS with an incidence ranging from 1.4 to 22 in 1000 births respectively in low and high risk populations (Achiron et al., 1993). It can result from various processes leading to differences in outcome and the presence of associated malformations ranges from 10 to 76% (Gaglioti et al., 2009). Proper criteria to measure the lateral ventricle (Fig. 2) have been proposed by Guibaud relating to the ideal axial plane to use, the identification of the proper landmarks in the axial plane, the surge for the internal parieto-occipital sulcus as optimal landmark and finally the optimal placement of the calipers in a sufficiently enlarged image (Guibaud, 2009). In normal conditions, the lateral ventricle at the level of the atria is slightly but significantly larger in male fetuses (Salomon et al., 2007). Ventriculomegaly is associated with chromosomal abnormalities in 3-15% of the cases (Gaglioti et al., 2009) and an abnormal neurological outcome has been observed in about 4% and 14% of cases with mild (10-12 mm) and moderate (> 12-15 mm) isolated ventriculomegaly respectively (Arora et al., 1998; Pilu et al., 2007).
More recently, Signorelli et al. (Signorelli et al., 2004) considered isolated mild ventriculomegaly as a variant of the normal since none of their cases showed neurological impairment on long-term follow-up. In addition, in 30% of the cases a reduction or normalization of the atrial width was noticed.

At school age, children with antenatally diagnosed isolated mild ventriculomegaly (≤ 15 mm) had normal visual, motor and perceptual abilities in 16 out of 17 cases (Weichtert et al., 2010; Colitto et al., 2009). There is no good evidence to suggest that the width of the ventricular atria contributes to the risk of neurodevelopmental outcome in fetuses with mild ventriculomegaly. The most important prognostic factors are the association with other abnormalities that escape early detection and the progression of ventricular dilatation, which are reported to occur in about 13% and 16% of cases, respectively. Most infants with a prenatal diagnosis of isolated mild ventriculomegaly have normal neurological development at least in infancy. The rate of abnormal or delayed neurodevelopment in infancy is about 11%, and it is unclear whether this is higher than in the general population (Mechiorre et al., 2009-2010).

Prospective evaluation of the long-term (3-72 months) neurodevelopmental outcome in isolated ventriculomegaly up to 15 mm showed a normal outcome in 81 to 100% of cases (Falip et al., 2007; Vergani et al., 1998; Breeze et al., 2005). In addition, unilateral isolated ventriculomegaly and asymmetric ventricles seem to represent a substantial risk for behavioural abnormalities and neuropsychiatric disorders (Sadan et al., 2007; Gilmore et al., 2008).

Fetal MRI is not indicated to confirm the presence of ventriculomegaly, but might be helpful in showing associated anomalies which may be missed by ultrasound, such as foci of infarction, abnormal myelination or cortical anomalies (Fig. 3) (Benacerraf et al., 2007; Denis et al., 2000).

Additional malformations not found by prenatal ultrasound can be detected in 5% to 44% (Salomon et al., 2006; Morris et al., 2007; Ouahba et al., 2006). Newer MRI techniques like diffusion tension imaging tractography and connectomics may be able to associate mild ventriculomegaly to permanent alterations in the cortical gray and white matter development (Gilmore et al., 2008; Mitter et al., 2011).

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**Fig. 2.** — Measurement of the lateral ventricle

**Fig. 3.** — MRI axial view of ventriculomegaly associated with bilateral polymicrogyria (encircled in white). Gestational age 27 weeks.
Choroid Plexus Cysts (CPC)

The choroid plexus is responsible for the production of cerebrospinal fluid. From week 6-7 onwards the choroid plexus develops in the roof of the fourth ventricle, in the lateral ventricle and finally in the third ventricle. It grows rapidly and by week 9 it fills > 75% of the cavity of the lateral ventricle. The sonographic appearance of a CPC is a sonolucent structure within the hyperechogenic choroid plexus (Fig. 4). They are usually small ranging from 3 to 20 mm and they have well delineated borders in the choroid plexus. They can be either uni- or bilateral. CPC’s are usually isolated findings but once diagnosed a targeted ultrasound should be performed. CPC resolve by 26-28 weeks. Malformations associated with CPC include omphalocele, congenital heart disease, renal abnormalities, cystic hygroma, hydrocephalus. These malformations are also

Fig. 4. — Large, but isolated choroid plexus cyst (arrow head) mimicking a ventriculomegaly.

Fig. 5. — Spinal neural tube defects are mainly detected by the presence of the “lemon” (yellow arrows) and “banana” sign (dashed arrows), or scalloping of the frontal bones and obliteration of the cisterna magna with hypoplasia of the cerebellum (a). Severe lesions are characterized by spinal dysraphism and are more easily detectable at the level of the spine itself (b). MRI axial view of a fetal meningomyelocele in a mother with a body mass index of 42. Gestational age 20 weeks (c).
reported in trisomies 18 and 21, cri du chat (5p-) syndrome and mosaic trisomy 9 (Gross et al., 1995; Samo et al., 1993). In the presence of CPC and other malformation there is a general consensus that genetic counseling and testing are indicated but there is disagreement regarding isolated CPC. In a karyotypically normal fetus, the presence of isolated CPC is not associated with any neurological sequelae such as mental retardation or delayed development. Even detected postnatally they have no major clinical significance.

Spinal Neural tube defects

The prevention of neural tube defects (NTD) by the pre-conceptual intake of folic acid, although efficient (Blencowe et al., 2010; Wilson et al., 2007), is hard to establish since over 50% of conceptions are unplanned. The use of maternal serum alfa-feto protein (AFP) (Wald et al., 1974) and subsequent amniotic fluid AFP lacks sensitivity and specificity (Dashe et al., 2006; Kooper et al., 2007) and will only detect the majority of open NTD (Wald, 2010). The introduction of the “fruit signs” to screen for NTD (Nicolaides et al., 1986) has increased the detection rate to nearly 90% in routine practice and to nearly 100% in tertiary care centers (Dashe et al., 2006; Cameron et al., 2009). The scalloping of the frontal bones (lemon sign) and the obliteration of the cisterna magna related to the descent of the cerebellum resulting in a curved hypoplastic cerebellum (banana sign) are very powerful tools before 24 weeks of gestation (Fig. 5a). Secondary signs like clubfeet may even increase the suspicion for open NTD. The cranial signs and the identification of the spinal lesion on ultrasound made the use of amniotic fluid AFP and acetylcholinesterase obsolete in the diagnosis of NTD. With 2D- and 3D ultrasound as well as with fetal MRI (Appasamy et al., 2006; Van der Vossen et al., 2009) the level of the lesions can be accurately determined. Fetal MRI may be useful particularly in those cases with limited amount of amniotic fluid, fetal malposition and obesity (Fig. 5c) (Glenn et al., 2006). Open neural defects are nearly always associated with Chiari II malformations, which can easily be depicted on MRI. Fetal MRI is also helpful to detect associated anomalies and to screen for potential candidates for fetal surgery. Although the degree of neurological impairment does not always correlate with the level of the defect (Kolias et al., 1992; Coniglio et al., 1996; Rintoul et al., 2002), the correct identification of the level of the lesion relates to neonatal survival (Van der Vossen et al., 2009), the ambulatory status, and bladder morbidity (Appasamy et al., 2006). The majority of children with lesions at or below L4 are ambulatory, but may present bladder and bowel incontinence (Cameron et al., 2009).

Detection of NTD in the first trimester depended largely on targeted scanning (Blumenfeld et al., 1993; Bernard et al., 1997; Hernádi et al., 1997). Now, disappearance of the intracranial translucency, normally found on a mid-sagittal view anteriorly to the occipital bone at the 11-13 weeks scan, may be used as a screening tool (Chaoui et al., 2009; Egle et al., 2011). In an era of emerging fetal therapies, correct and timely selection of patients using different well established imaging criteria and work-up through additional investigation will optimize patients selection for in utero sealing of the spinal defect. Fetal surgery seems to reduce the need for...
postnatal shunting with 40% and improves motor function at the age of 30 months with 66% (Adzick et al., 2011), although the optimal uterine access has yet to be established (Kohl et al., 2009).

Midline malformations

Semilobar and alobar holoprosencephaly can be diagnosed in the first trimester of pregnancy (Volpe et al., 2009). Failure of the prosencephalon to divide leads to a single ventricle and a fusion of the thalami. The falx cerebri, cavum septi pellucidi and corpus callosum are absent. There is often a variable degree of mid-facial maldevelopment, ranging from anophthalmia to hypotelorism to a normal face (Volpe et al., 2009; Blaas et al., 2002; Dubourg et al., 2007; De Meyer et al., 1964) (Fig. 6). In the milder lobar holoprosencephaly there is a partial fusion of the anterior horns of the lateral ventricles, no cavum septi pellucidi, a partially absent corpus callosum and fusion of the fornices (Pilu et al., 1994; Hahn et al., 2010).

Early diagnosis of holoprosencephaly by 3D ultrasound has been suggested (Timor-Tritsch et al., 2008). The 3D surface rendering mode may help to define the extent of the facial lesions and additional malformations. There are a well known associations with chromosomal abnormalities, genetic mutations, various syndromes and environmental factors. The recurrence risk varies accordingly (Dubourg et al., 2007; Mercier et al., 2010)).

Failure of the prosencephalic midline development results in disorders of the corpus callosum, septo-optic dysplasia and absence of the septum pellucidum (Volpe et al., 2009). About 5/1000 births are affected by corpus callosum agenesis (CCA), which may be due to a variety of causes and conditions: chromosomal defects, genetic syndromes, metabolic and environmental conditions (Volpe et al., 2009; Pilu et al., 1993). Complete CCA can be suspected on the standard transthalamic image of the fetal brain by the absence of a normal cavum septum pellucidum, teardrop shaped lateral ventricles (Pilu et al., 1993), colpocephaly and dilatation of the third ventricle. Even isolated, a significant neurodevelopmental delay may occur in 15-36% of the cases (Pilu et al., 1993; Fratelli et al., 2007). The presence of other cerebral and extra-cerebral malformations worsens the prognosis. Differentiation between complete agenesis, hypoplasia of partial formation of the CC can only be established by mid-sagittal exploration of the brain (Volpe et al., 2006; Ghi et al., 2010). Normally, the complete visualization and measurement of the CC is feasible from 18 weeks gestation onwards (Malinger et al., 1993). Investigation by color Doppler identifies the pericallosal artery and its branching, which is deranged when the CC is abnormal or absent (Fig. 7). Tomographic 3D ultrasound imaging enables easy evaluation of the mid- and parasagittal planes (Pilu et al., 2006; Plasencia et al., 2007; Merz, 2010).

Midline malformations are good candidates for further characterization and/or classification on fetal MRI. Second trimester MRI is ideal to assess the presence and extent of cortical non-separation, the presence of fusion of the basal ganglia or hypothalamus and to identify the absence or presence of structures such as the interhemispheric fissure, the Sylvian fissure, the falx and the septum pellucidum. The presence of cortical dysplasia or gray matter heterotopia can also be detected on MRI. In case of CCA, MRI is mainly used to detect additional anomalies. Moreover, fiber tracking fetal MRI studies and functional MRI may hold the future for differentiat-

Fig. 7. — Absent cavum septum pellucidi, teardrop shaped ventricles and an abnormal underdeveloped pericallosal artery pattern illustrated by color Doppler flow are characteristic for agenesis of the corpus callosum.
Routine exploration of the posterior fossa (PF) includes the evaluation of the cerebellum, the vermis and the cisterna magna, and is of major importance since its involvement in more than 100 syndromes (Online Mendelian). However, ultrasound diagnosis of PF anomalies is challenging as many studies have shown a discordance between sonographic diagnosis and pathological correlation (Carroll et al., 2000; Forzano et al., 2007; Kapur et al., 2009). Pitfalls in the diagnosis of PF anomalies have been attributed to confusion in terminology describing vermian pathology, the gestational age at diagnosis, the incorrect assessment of the midsagittal plane of the cerebellum and the late development of some of the pathological conditions (Malinger et al., 2009). More detailed exploration by transvaginal ultrasound (Malinger et al., 2001), the measurement of the fourth ventricle, the fastigium and vermis, the assessment of its angle and the appearance of the primary fissure by a 3D midline view may contribute to the diagnosis of subtle posterior fossa anomalies (Pilu et al., 2006; Goldstein et al., 2002; Zalel et al., 2002; Paladini et al., 2006; Tepper et al., 2009; Zalel et al., 2009). Differentiation of PF midline anomalies, the Dandy-Walker complex, has been revised recently (Malinger et al., 2009). Reliable interpretation of the normal development and growth of the cerebellar vermis is possible from 18 weeks onwards (Hahn et al., 2010; Zalel et al., 2006). The Dandy-Walker spectrum consist of the megacisterna magna, Blake’s pouch cyst (Calabrò et al., 2000), hypoplasia and complete agenesis of the vermis. Blake pouch cyst represents posterior ballooning of posterior medullary velum into the cistern magna, below and posterior to the vermis. It is thought to be secondary to a failure of perforation of the foramen of Magendie. Features include a fourth ventricle communicating with the cyst, which does not communicate with the cisterna magna. There is usually no vermian hypoplasia and no elevation of the tentorium cerebelli. MRI can encompass several limitations encountered by sonography, such as problems of visibility caused by acoustic windowing of bony structures and the difficulty to obtain a perfect mid-sagittal view of the brain (Fig. 8). In addition, MRI excels in obtaining morpho- and volumetric measurements of the cerebellar hemispheres and vermis.

Destructive lesions

Hydranencephaly results from obliteration of the internal carotid artery. The result is either a massive infarction with liquefaction necrosis of one or both hemispheres. Schizencephaly on the contrary, is now considered a neuronal migration disorder related to the complete agenesis of a portion of the germinative zones (Volpe, 2000).

Congenital CMV results in the highest incidence of children born with or developing long-term neurological morbidity (Gaytant et al., 2002; Kenneson et
al., 2007; Boppana et al., 2005; Andriesse et al., 2006; Kylat et al., 2006; Foulon et al., 2008), with a burden in the USA twice as high as compared with fetal Down syndrome, spina bifida or fetal alcohol syndrome (Cannon et al., 2005). Periconceptual and first trimester primary infection have a vertical transmission rate of 30% and are responsible for about 10% severe morbidity and mortality and another 5 to 10% of minor disabilities (Kenneson et al., 2007; Ludwig et al., 2009; Stagno et al., 1986; Fowler et al., 1992; Boppana et al., 2001; Ross et al., 2005; Peckham et al., 1987; Gindes et al., 2008). Fetuses affected by viral infections, like CMV, present a variety of non specific abnormalities (Degani, 2006; Guerra et al., 2008; Benoist et al., 2008). Cerebral ultrasound abnormalities include broad hyperechoic periventricular halo (Simonazzi et al., 2010), brain calcifications, microcephaly, hydrocephaly, cyst formation in the germinative matrix and intraventricular adhesions (Benoist et al., 2008; Guibaud et al., 2004; Malinger et al., 2003; Picone et al., 2008). More difficult to demonstrate on ultrasound and hence a good indication for MRI is the detection of polymicrogyria, cerebral hypotrophy, cerebellar and vermian hypoplasia, hypoplasia of the CC and leucomalacia (Dhombres et al., 2008; Doneda et al., 2010) (Fig. 9). Also the typical CMV related cystic foci of brain destruction around the temporal horn of the lateral ventricles, are best depicted on MRI. Targeted transvaginal ultrasound may facilitate the detection of minor lesions (Soussotte et al., 2000). The prediction of brain anomalies in infected fetuses is relatively accurate (sens 86%, spec 85%) (Benoist et al., 2008). If proof of fetal infection has been delivered, odds ratio for poor outcome in the presence of non cerebral and cerebral ultrasound

Fig. 10a. — Vascular anomalies are uncommon, but the most frequently seen on prenatal ultrasound is the arteriovenous malformations of the vene of Galen. 3D color Doppler imaging allows to create a 3D rotational cast of the A-V malformation.

Fig. 10b. — MRI midsagittal view at gestational age 31 weeks (left) and 36 weeks (right) of an aneurism of the Galen vein (arrow head).
malformations are respectively 7.2 and 25.5 (Benoist et al., 2008). Microcephaly, cortical malformations and intraparenchymal cysts show a strong correlation with poor outcome (OR: 25.5 (6.4-101.9)) (Benoist et al., 2008; Malinger et al., 2003). Fetal MRI may increase the detection of white matter lesions and polymicrogyria (Benoist et al., 2008; Picone et al., 2008; Doneda et al., 2010), and most often correlates well with the ultrasound findings (Fig. 9). Although some trials on maternal CMV prevention by vaccination look tempting (Pass et al., 2009), a universal vaccination program to eradicate CMV infection remains challenging. Regression of cerebral as well as non-cerebral ultrasound lesions in fetuses after primary CMV infection has been observed after maternal infusions with hyperimmune globulins (Nigro et al., 2008). Randomized studies evaluating the benefit of either prenatal administration of specific anti-CMV immunoglobulins (Nigro et al., 2008; Nigro et al., 2005; Adler et al., 2009) or antiviral drugs (Jacquemard et al., 2007) have been proposed recently.

Vascular malformations

Congenital arterio-venous malformation of the choroidal system represents less than 1% of all intracranial vascular lesions. The aneurism of the vene of Galen results from an abnormal connection of one or multiple arteries into the prosencephalic vein, resulting in dilatation of the vein, the straight sinus, the confluens and the transverse sinuses (Gupta et al., 2004).

Often this malformations results in a high cardiac output failure. Color Doppler flow imaging allows for the identification of the dilated venous system

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**Fig. 11a.** — A suprasellar arachnoid cyst (arrow head) exerts pressure of the circle of Willis and the optic chiasma. Power Doppler imaging shows the extension of the circle of Willis at the base of the cyst.

**Fig. 11b.** — MRI axial (left) and coronal (right) view of a voluminous mixed solid-cystic lesion in the left cerebrum. Note the shift of the midline to the contralateral side. Postoperative biopsy revealed a glioblastoma.
and the turbulent flow in the A-V malformation, and easily differentiates the conditions from other cystic lesions in the brain (Fig. 10a). Prenatal MRI (Fig. 10b) offers the advantage of a large field of view and it is sometimes preferred to compare the evolution of the vascular anomaly with postnatally acquired brain MRI scans. Bad prognostic signs include cardiac high output failure, fetal hydrops and leucomalacia (Yuval et al., 1997). Primary treatment in the neonatal period consists of transfemoral arterial embolization with N-butylcyanoacrylate, resulting in a survival rate of about 50% and a 36% normal neurological development (Lasjaunias et al., 2006).

Intracranial tumors and cysts

Over 50% of intracranial tumors are teratomata (Köken et al., 2008), causing macrocrania and hydrocephaly. Occasionally polyhydramnios develops. Teratoma usually present late in the third trimester as fast growing heterogeneous solid-cystic masses with calcifications. It has to be differentiated from craniopharyngioma, glioblastoma and astrocytoma. The extend of the lesions can be evaluated by tomographic ultrasound and MR imaging. The specificity of ultrasound in the detection of fetal intracranial tumors is 86%. The accuracy of identifying the histological type is limited to 57% (D’Addario et al., 1998). The most common cystic lesions are arachnoid cysts, which are usually asymptomatic. However if large, ventriculomegaly may result. Differentiation from papilloma of the choroid plexus and gliopendymal cysts remains difficult (Pelkey et al., 1997). Large suprasellar arachnoid cyst cause compression of the optic chiasma and circle of Willis (Fig. 11a), and may be responsible for endocrinological dysfunction. Fetal MRI helps to determine the nature of the tumoral mass, the extent of involvement and the prenatal planning of emergency postnatal neurosurgery (Fig. 11b).

Intracranial hemorrhage

Prenatal intracerebral hemorrhage grading is comparable to the grading used in newborns (Table 2). Recent intraventricular bleeding (IVH) presents as a
echogenic intraventricular mass, disappearing rather rapidly due to liquefaction. Echogenic irregular lining of the lateral ventricle and ventriculomegaly may persist long after the initial bleeding (Fig. 12a). Occasionally only ventriculomegaly is noticed, and a confident diagnosis of IVH can only be made by fetal MRI (Zanders et al., 2003). For the detection of small blood remnants or hemorrhagic foci MRI is the best modality (Fig. 12b). Determining the etiology of the bleeding is difficult and often impossible; investigation should be focused on coagulation disorders, congenital infections, immune thrombocytopenia, ischemic insults and trauma (Zanders et al., 2003). Prognosis is poor particularly in parenchymal and subdural bleeding, with a normal neurological outcome in 52% of the cases and a severe handicap in 27% of the cases. The worse outcome is associated with IVH III and IV (Ghi et al., 2003).

Neuronal proliferation disorders

Proliferation disorders of the brain are often characterized by microcephaly, which is defined as a head circumference less than 3 SD from the mean (Malinger et al., 2003; Dahlgren et al., 2001). The etiology is heterogeneous and can be related to chromosomal defects, genetic disorders, recognized syndromes and environmental insults (Dahlgren et al., 2001). The prenatal diagnosis is difficult and often made late in gestation. Besides head biometry, structured analysis of the brain enables the detection of morphologic derangements often associated and transvaginal sonography and power Doppler are powerful tools in the assessment (Pilu et al., 1998).

MRI is particularly helpful in detecting gyral anomalies and foci of heterotopias. A good example of the additional value of fetal MRI is the detection of brain lesions in patients with a tentative prenatal diagnosis of tuberous sclerosis.

Schizencephaly is a neuronal migration anomaly characterized by a cleft lined by heterotopic gray matter that extends from the ependyma of the lateral ventricles to the surface of the cortex resulting from a genetic mutation or secondary to destruction of immature brain before neuronal migration (Denis et al., 2000). In contrast to previous concepts, this malformation is considered as a deviation from the normal development rather than a destructive process of mature cortex. MRI is needed to differentiate this entity from porencephaly (Benacerraf et al., 2007). Schizencephaly may be uni-or bilateral and is classically located in the distribution of the middle cerebral artery.

Conclusion

Recent evolution in ultrasound equipment enables a more refined diagnoses of most congenital malformations of the brain. Only through a structured analysis of the fetal CNS anatomy, even rare conditions may be detected more often. Although some brain anomalies are only visible late in gestation there is a strong tendency towards a more detailed neurosonogram in the second or even first trimester of pregnancy. 3D ultrasound is a valuable tool in detailed structural analysis of the brain. The acquisition and storage of 3D data sets enables easy offline review of the data volumes and facilitates second opinions of specialists in the field. Additional cytogenetic and infectious investigation is mandatory in the majority of cases of ventriculomegaly and hydrocephaly. Fetal MRI has been shown to particularly helpful in the assessment of the gyration, disorders of gray and white matter, and intraventricular bleeding and migration disorders. Evaluation of all aspects of the condition by a multidisciplinary team should precede parental counseling.

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