Main Congenital Cerebral Anomalies: How Prenatal Imaging Aids Counseling

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Key Words

Fetus · Brain · Prenatal diagnosis · Prenatal counseling · Corpus callosum · Septal agenesis · Posterior fossa · Hemorrhage

Abstract

The purpose of this article is to discuss some common cerebral lesions that may be detected during prenatal screening: corpus callosum dysgenesis, absent septum pellucidum, localized parenchymal ischemic-hemorrhagic lesions, megacisterna magna, Blake's pouch cyst, posterior fossa arachnoid cyst and Dandy-Walker malformation. For each cerebral defect, the main imaging findings are reminded, certain differential diagnoses are discussed and prenatal diagnostic accuracy is analyzed with emphasis on uncertainties encountered during analysis of ultrasound or magnetic resonance images. Detecting cerebral lesions in fetuses requires rapid counseling by neuropediatricians. Keeping in mind that the prenatal diagnostic accuracy is not 100%, the neuropediatricians have to answer the parents' questions regarding the outcome of the unborn child as well as the risk of recurrence for future pregnancies. This article is based on the authors' large experience in both prenatal imaging and neurocounseling. The frequently asked questions are set up. Answers are provided, underscoring the importance of an appropriate description of the cerebral defect, and therefore the piv-

otal role of prenatal imaging. However, prenatal neurocounseling remains challenging and the parents must be aware of uncertainties regarding both diagnostic accuracy and prognostic evaluation.

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Cerebral malformations are commonly detected during prenatal screening. Announcing to the future parents that a cerebral defect has been observed in their baby is particularly scary and usually generates many questions, requiring rapid counseling. The purpose of this article is to focus on some common cerebral anomalies and for each of them: to remind how the diagnosis may be achieved by prenatal imaging and which uncertainties the sonographers face, to set up the main questions asked by the parents and which details neuropediatricians need to answer these questions.

Although ventricular dilatation is the most common cerebral abnormality detected by prenatal imaging, this topic will purposely not be addressed. Indeed, many review articles have already been published on this topic and some of them have focused on the answers to the frequently asked questions regarding this diagnosis [1].

It must be kept in mind that the diagnostic accuracy of prenatal cerebral imaging is not 100%, disagreement between pre- and postnatal imaging with a prognostic im-

Fig. 1. Partial callosal agenesis. Patient referred at 30 weeks of gestation for ventriculomegaly; US (a) and MRI (b) were performed on the same day and showed partial CCA associated with opercular dysplasia (not shown). The anterior part of the CC (arrow) is better delineated on US than on MRI. The rostrum is missing and the genu is hypoplastic (this was confirmed by neuropathology performed after termination of pregnancy). Conversely, the posterior part of the CC (dotted arrow) is much better depicted on MR images.

pact being observed in about 9% of cases [2]. Taking into account the gestational age is also important as the diagnostic accuracy of some cortical malformations is lower in young fetuses [3].

The following lines are based on the literature but also and mainly on the authors' more than 20-year experience in prenatal imaging (C.G.) and neurocounseling (M.-L.M.).

Corpus Callosum Dysgenesis

How Can the Prenatal Diagnosis of Corpus Callosum Dysgenesis Be Achieved?

The diagnosis of complete corpus callosum (CC) agenesis (CCA) is based upon well-known direct (non-visualization of the CC) and indirect findings: absent CSP, upward displacement of the third ventricle, lateral displacement of the lateral ventricles and parallelism of the atria, radial pattern of the sulci of the internal aspect of the hemispheres. Colpocephaly is commonly observed [4]. Partial CCA is suspected when the CC appears too short [5]. Its shape should be analyzed and, specifically, its frontal part (rostrum present or not?). Its length should be evaluated and compared with reference charts [6]. Hypoplastic or thick CC is suspected when the CC appears too thin or too thick, respectively. Ultrasound (US) examination may also show interhemispheric cyst or pericallosal lipoma, associated with CC dysgenesis.

What Is the Contribution of Magnetic Resonance Imaging for the Diagnosis of CC Dysgenesis?

It is entirely dependent on the sonographer's experience and the conditions of the US examination. It has

been reported that the US diagnosis of CCA is associated with a false-positive rate of 0–20%, thus underlying the contribution of magnetic resonance imaging (MRI) [4]. The anterior part of the CC is usually better delineated by US (using an anterior transfontanellar approach) while the posterior part is better depicted by MRI (fig. 1). Therefore, some very partial types of CCA with only a small part of the genu being present are better seen with US and are sometimes visible only after birth [2]. Conversely, thin CC is better delineated with MRI [7].

How Accurate Is Prenatal Imaging in the Detection of Associated Cerebral Anomalies?

This is undoubtedly the most important contribution of MRI in the setting of CC dysgenesis. MRI has been reported to detect additional abnormalities in 22.5% of cases compared with US [8]. We share this experience (fig. 2).

Is Imaging Reliable to Determine if CCA Is Isolated or Not?

According to many authors – particularly in the articles written during the past decade – CCA is considered isolated when prenatal workup including MRI and genetic tests does not reveal any additional anomaly [5, 9–11]. In fact, a positive family history (mental retardation, epilepsy and/or psychiatric disorders), parental consanguinity or certain abnormal findings observed during the pregnancy (such as nuchal anomaly, intrauterine growth retardation, infection, drug or alcohol addiction or reduced fetal movements) have to be carefully searched for. When such findings are present, CCA is probably syndromic or part of a genetic, metabolic or infectious disease.

Fig. 2. Complete callosal agenesis associated with nodular subependymal heterotopia. Patient referred at 36 weeks of gestation for complete callosal agenesis detected a week earlier; US (**a**, **b**) and MRI (**c**, **d**) were performed on the same day. The radial pattern of the sulci of the internal aspect of the hemispheres is well depicted by both imaging modalities (**a**, **c**). Heterotopias (arrows) are better delineated on MR images (**d**) than on US images (**b**).

Does the Prognosis Depend on CCA Being Partial or Complete?

In our study focusing on children presenting with isolated CCA and with a 10-year follow-up [12], we found no statistically significant difference between partial or complete CCA. Children with partial CCA tend to score better in psychometric tests. Few studies are dedicated to the outcome of prenatally diagnosed partial CCA only, because until the early 2000s, the distinction between partial and complete CCA was usually not established by prenatal imaging. Goodyear et al. [13] have reported a good outcome in children with partial CCA but cases with pre- and postnatal diagnosis were not evaluated separately. Volpe et al. [14] found that the outcome of children with isolated partial CCA was similar to those with isolated complete CCA. However, due to the small number of cases in each study, it remains difficult to evaluate the outcome of CCA according to the type of agenesis.

Is Ventriculomegaly Considered an Associated Finding and Does It Impact on the Prognosis?

Ventriculomegaly (VM) is part of the CCA malformation and should not be considered an associated finding

that worsens the prognosis. It is usual to observe an enlarged atrial diameter that may reach 20 mm. Conversely, a severe and progressive ventricular dilatation is abnormal and particularly in a male fetus, with adducted thumbs, it should raise the diagnosis of a MASA syndrome.

Has the Fetal Sex a Prognostic Impact?

In our study [12] focused on the outcome of a fetus with isolated CCA, we did not observe any prognostic impact of the fetal sex. In the literature, there are no data regarding a possible correlation between fetal sex and long-term neurodevelopmental outcome [8].

Do Certain Associated Malformations Carry a Better Prognosis?

CCA may be observed in the setting of genetic and metabolic diseases, whose outcome is usually poor. However, some associated malformations (such as polydactyly or pyelectasis) are probably found incidentally and do not worsen the prognosis. Moreover, certain brain malformations such as interhemispheric cysts or, less often, pericallosal lipomas are often associated with partial or complete CCA. Children presenting with these malformations have

usually a normal neurodevelopmental outcome. However, late-onset epilepsy can occur in large interhemispheric cysts (related to polymicrogyria lining the cyst) [15] or in tubulonodular lipomas.

When CCA Is Isolated, What Is the Children's Outcome?

A review article [8] was recently dedicated to neurodevelopmental outcome in truly isolated CCA. In this field, only six studies using appropriate data (MRI before and after birth, neurodevelopmental assessment with standardized tests) are available in the literature. The outcome is reported to be favorable in 75.4% of cases, moderate disability is observed in 13%, and severe disability in 11.6% of cases. In our study, 75% of the children had a normal intelligence but could present with school difficulties or specific troubles such as dyslexia; 25% of children had a borderline intelligence, with important difficulties at school and early orientation to a 'simple' job. It is noteworthy that there was a significant correlation between children with borderline intelligence and poor maternal educational level.

Is There a Risk of Recurrence?

The risk of recurrence is correlated to the underlying cause of CCA: about 15 genes have been identified as responsible for CCA and approximately 250 syndromes include CCA without known genetic implication. Regarding isolated CCA, most of the cases are sporadic [11]. However, an autosomal recessive or dominant transmission is rare (about 3% in our experience). It might justify systematic MRI assessment of the parents' CC.

Absence of Septum Pellucidum

Absence of septum pellucidum (ASP) may be observed in septal agenesis (SA) or disruption. Indeed, marked VM, or sudden increase in intraventricular pressure or ischemic-hemorrhagic lesions may cause mechanical necrotic disruption of the septum pellucidum. ASP may be isolated or associated with schizencephaly, or observed in the setting of septo-optic dysplasia (SOD) (optic tract hypoplasia and/or hypothalamic-pituitary dysfunction).

How Can the Prenatal Diagnosis of ASP Be Achieved?

The diagnosis of ASP is based on the identification with US of square fused frontal horns with low-set fornix (fig. 3). ASP may be partial or complete. SA may be as-

sociated with ventricular dilatation. MRI is not useful for assessing this diagnosis as it is easily achieved on US coronal views. In septal disruption, the septum is fenestrated in association with VM (fig. 4). In those cases, the ventricular size is reported to be significantly larger than in SA [16]. However, in our experience, when VM is isolated (absence of hemorrhagic and/or ischemic lesions), it may be exceedingly difficult with US and MRI to differentiate SA and septal disruption.

How Accurate Is Prenatal Imaging in the Detection of Associated Cerebral Anomalies?

Schizencephaly may be diagnosed by US in open-lip types while closed-lip schizencephalies are better visualized by MRI [7].

Diagnosing SOP in fetuses is challenging for two reasons: the optic pathways are very thin structures, which are very difficult to evaluate properly either with 3D US [17] or with MRI [7]. The pituitary gland and stalk are visible with MRI, but subtle abnormalities are likely to be overlooked [7]. Isolated prenatal cases of abnormal optic pathways associated with SA have been reported [16–18] (fig. 5).

Is VM Meaningful?

VM is a common finding, observed in ASP in association with schizencephaly or in the setting of a disruptive process [16]. The main concern is whether VM carries a poor prognosis in isolated or apparently isolated ASP. In the study of Li et al. [16], 5 cases only were considered isolated prenatally, but in 3 cases, major malformations or chromosomal anomalies were diagnosed postnatally. In the remaining 2 cases, 1 child had an important VM with aqueductal stenosis and showed a normal psychomotor development. The second child presented with frontal horn dilatation only and the diagnosis of polymicrogyria was achieved after birth. He showed a mild developmental delay at 1 year of age. Another study [19] focused on the outcome of true isolated ASP; no difference was observed according to the ventricular diameter when it was inferior to 15 mm, the outcome being favorable in all cases. Therefore, moderate VM does not seem to worsen the prognosis of ASP. Moreover, VM is not a reliable finding that may help suggest a SOD. If VM is slightly progressive or superior to 15 mm, the fetal brain should be carefully analyzed, in order to search for an associated aqueductal stenosis, or intraventricular hemorrhage (IVH) that could require postnatal ventricular shunting and usually carry a good prognosis.

Fig. 3. SA. US (**a, b**) and MRI (**c, d**) performed at 34 weeks of gestation and showing the typical square fused frontal horns. The low-set columns of the fornix (arrow-heads) are well visualized on US images. The optic chiasm (arrow) is well depicted on the T2-weighted midline sagittal slice (**d**).

Fig. 4. Septal disrupture. Patient referred for US at 23 weeks of gestation for marked dilatation of the lateral ventricles. The dilatation of the third ventricle is less prominent. The axial (**a**), coronal (**b**) and sagittal (**c**) images show abnormal communication (star) be-

tween the frontal horns, resulting from septal disrupture. No findings in keeping with IVH were observed. However, after termination of pregnancy a week later, the neuropathological examination revealed IVH of different ages.

Is There a Difference between Partial or Complete ASP?

There are no data available regarding a possible different outcome according to isolated ASP being complete or partial; in the study of Damaj et al. [19], complete agenesis seemed to carry a better prognosis but the number of partial ASP was too small to be statistically significant.

Which Counseling?

Counseling a couple whose fetus presents with an apparently isolated ASP remains challenging, as no imaging and no prenatal genetic test can help to definitely rule out SOD. Moreover, SOD presents a wide phenotypic range: when the syndrome is complete (ASP, optic atrophy, en-

Fig. 5. Septo-optic dysplasia. Patient referred for MRI at 32 weeks of gestation following the detection of SA. On the T2-weighted midline sagittal slice (**a**), the optic chiasm is not seen (compared with fig. 3d). It is visible (black arrow) on the coronal slice (**b**) but appears very thin. On the T1-weighted midline sagittal slice (**c**), the pituitary gland (white arrow) is well depicted and appears hyperintense (no difference between anterior and posterior pituitary glands).

doocrine dysfunction), children are at risk for mental retardation, while children with dissociated findings, which is more frequent, have a more favorable outcome (normal development or moderate developmental delay). Lepinard et al. [18] suggested to measure estriol in the maternal blood and urine in order to evaluate fetal adrenal function; however, in common practice, this test is not performed probably because it does not contribute to evaluate precisely the type of SOD. Involvement of the optic tract carries a much poorer prognosis than endocrine dysfunction. Children with isolated ASP have a favorable neurological outcome [19, 20], but 18% of fetuses diagnosed with ASP are at risk for SOD. Therefore, counseling the parents implies taking into account this possibility, explaining the treatment required by endocrine deficiencies, and the lack of therapeutic possibility in case of optic atrophy. In our experience, despite the risk of SOD, many parents elect to continue the pregnancy. After birth, glycemia has to be checked regularly during the first 2 days, as growth hormone deficiency may be responsible for repeated neonatal hypoglycemia. Endocrine assessment and ophthalmological examination are mandatory during the first 2 months of life in all children diagnosed with apparently isolated ASP.

Is There a Risk of Recurrence in Future Pregnancies?

When ASP is associated with brain malformation, chromosomal anomalies, or hydrocephaly, the risk de-

pends on the underlying pathology. In case of schizencephaly, familial cases suggest a genetic cause. Genes involved in the establishment of midline forebrain structures are considered possible candidates, and Hehr et al. [21] have reported heterozygous mutations in SIX3 and SHH, which belong to the holoprosencephaly spectrum.

So far, no gene has clearly been identified in SOD: Datani et al. [22] found mutations in HESX1 gene in rare cases of SOD; genes involved in optic nerve hypoplasia or in pituitary gland dysfunction may be responsible for some types of SOD.

Localized Parenchymal Ischemic-Hemorrhagic Lesions

The role of imaging is twofold:

- (1) *To diagnose the lesion:* focal ischemic damage may appear as cavitations or as hyperechoic lesions, which may be very difficult to differentiate from hemorrhage. Such lesions may be detected by US, but some areas cannot be imaged by the US beam due to the cranial vault or to insufficient contrast resolution (for instance, the temporal lobe of the far-field hemisphere). Therefore, MRI is very useful when ischemic-hemorrhagic damage is suspected in at-risk fetuses or following the detection of US abnormalities. MRI al-

Fig. 6. Hemorrhage related to COL4A1 mutation. Patient referred for MRI at 30 weeks of gestation for marked left ventricular dilatation with echogenic lining on US images, suggesting IVH. On these axial T2- (a), T1- (b) and gradient-echo T2-weighted sequences (c), the left ventricle is markedly enlarged and shows posterior marked hypointensity on T2* images (dotted arrow), consistent with IVH. Moreover, in the near-field hemisphere, a small ante-

rior right lesion is visible (arrows) and was missed by US. It appears T2 hyperintense, T1 hyperintense and is lined by marked hypointensity on T2* images, in keeping with hemorrhage. The small hypointense dots (arrowheads) located posterior to this lesion (c) correspond to hemorrhage deposits in the wall of the right ventricle.

lows evaluation of the entire cerebral parenchyma. The use of gradient-echo sequences makes it possible to identify old hemorrhagic lesions, which may be missed by US (fig. 6).

- (2) *To localize the lesion and evaluate its extension:* with US, it is possible to determine if the cerebral hemispheres or the cerebellum are involved. In case of supratentorial damage, it is important to evaluate the precise localization of the lesion (cortex and/or white matter) and its extension in relation to the main cerebral territories (fig. 7). If the lesion involves the posterior fossa, imaging must determine if the cerebellar hemispheres and/or the vermis are damaged. MRI is mandatory for such a work-up as it delineates more accurately than US the different supra- and infratentorial structures. However, in our experience, when one cerebellar hemisphere is severely damaged, the axis of the vermis is rotated so that it may be easier to evaluate the vermis by US than by MRI (as it is easier to gently tilt the US probe than to find the exact angle of the vermis on MRI slices).

What Are the Causes of Parenchymal Ischemic-Hemorrhagic Insults?

Except for the particular setting of monochorionic pregnancies, the causes of fetal parenchymal ischemic-hemorrhagic insults are numerous: maternal trauma, maternal history of drug exposure, chromosomal anomalies,

infection (TORCH) or platelet alloimmunization, thrombophilic disorders, underlying inflammatory or metabolic disease, etc. Recently, mutations in the COL4A1 gene have been reported to be responsible for IVH [23, 24] (fig. 6).

What Is the Prognosis?

The prognosis depends on the etiology but also on the lesion itself, accounting for the important role of fetal imaging. Different scoring systems have been established to predict the outcome of IVH [25, 26], depending mainly on the degree of VM, on IVH being uni- or bilateral and on the presence of adjacent brain damage.

In case of an ischemic-hemorrhagic parenchymal insult, the localization of the lesion impacts on the prognosis: for instance, a unilateral anterior frontal lesion, if limited, can carry a good prognosis, a unilateral cerebellar hemispheric insult may also have a good outcome if the vermis is not involved [27, 28]. Lesions involving the cortex are at risk for postnatal focal epilepsy; if the central sulcus is involved, a contralateral congenital hemiparesis is the rule (fig. 7). Lesions of the occipital lobe may generate visual disorders.

Bilateral, multifocal or extensive lesions worsen the prognosis and may be responsible for intrauterine fetal death; some etiologies, such as COL4A1 microangiopathy, are associated with severe ischemic-hemorrhagic insults [29].

Fig. 7. Porencephalic cavity. Patient referred for MRI at 34 weeks of gestation for right ventriculomegaly. On US (a) and MR (c) coronal slices, the right ventricle is enlarged and displays an abnormal square shape. On US (b) and MR (d) sagittal slices, the body of the right ventricle is enlarged and shows irregular borders, consistent with a porencephalic cavity communicating with the ventricle. This ischemic lesion faces the central sulcus (arrows) and consequently involves the pre- and post-central gyri. The surrounding parenchyma did not show any hemorrhage on the other sequences. The lesion is located in the deep white matter and does not seem to involve the cortex.

Fluid-Filled Space-Occupying Lesions of the Posterior Fossa with Normal Cerebellar Hemispheres and Brainstem

What Must Be Evaluated by Imaging?

The anteroposterior diameter of the retrocerebellar fluid space is often superior to 10 mm, unless the fluid space-occupying lesion is not located on the midline. As it may encompass different entities with very different prognoses, it is mandatory to evaluate with US and/or MRI according to the sonographer's experience and the conditions of the examination: (a) the position of the torcular and the orientation of the tentorium cerebelli, (b) the vermis: axis, foliation, size and morphology, (c) the echogenicity of the fluid-filled space-occupying lesion, (d) the presence and location of the walls of the Blake's pouch and the presence of septa within the lesion, and (e) the mass effect on the cerebellum, the tentorium and the occipital vault.

Which Entities May Be Found?

Megacisterna magna: normal position of the torcular and orientation of the tentorium, normal vermis, visibil-

ity of subarachnoid vessels within the fluid-filled space-occupying lesion, accounting for slight hyperechogenicity, visibility of the walls of the Blake's pouch delineating an anechoic space, possibility of mild mass effect on the cerebellum and the tentorium.

Blake's pouch: normal orientation of the tentorium, possible mass effect on the distal part of the tentorium, normal foliation and height of the vermis, rotation of its axis, possible mass effect on the inferior vermis, anechoic lesion delineated by echogenic walls of the Blake's pouch (the lateral walls are visible on a transverse slice and the superior border is visible on the midline sagittal view at the inferior and posterior part of the vermis).

Arachnoid cysts: possible marked mass effect on the distal insertion of the tentorium (normal location of the torcular), on the vermis and/or the cerebellar hemispheres and on the occipital vault; normal compressed vermis and or hemispheres (cysts may be asymmetrical), anechoic structure with possible septa, the walls of the cysts may be depicted by US or MRI.

Dandy-Walker malformation (DWM): elevated tentorium and torcular, rotation of the vermian axis, abnormal foliation, size and morphology of the vermis, anechoic

Fig. 8. Cyst of the quadrigeminal cistern. Patient referred at 35 weeks of gestation following the detection with US of a small cyst located in the quadrigeminal cistern. The cyst (arrow) is well demonstrated on the US coronal slice (a) and on the T2-weighted mid-

line sagittal slice (b). At 11 months of age, due to increased head circumference, the child underwent an MRI examination, which showed a dramatic increase in size of the cyst [T1-weighted mid-sagittal slice (c)] requiring shunting.

structure communicating with the fourth ventricle and lined by the Blake's pouch walls (visible on transverse and midline sagittal views) [30, 31].

Whatever the imaging modality used, it may be difficult to differentiate a Blake's pouch and a partial vermian agenesis (when the walls are not visible) or a megacisterna magna and a retrocerebellar cyst (if the mass effect is not marked). It may also be uneasy to evaluate properly the extent of the vermian dysgenesis in a DWM when the cyst exerts an important mass effect on the vermis.

What Is the Outcome of Megacisterna Magna?

Megacisterna magna is more frequent in males (sex ratio 3.75/1); it may be associated with chromosomal anomalies, CNS or extra CNS malformations in up to 62% of cases [32, 33]. When isolated, MCM has a favorable outcome in 92–100% of cases; associated mild VM is commonly observed and carries a good prognosis [32, 34, 35].

What Is the Outcome of Blake's Pouch Cysts?

Isolated Blake's pouch cysts have no consequences on neurodevelopment. The main concern is to rule out inferior and posterior vermian agenesis. Cysts markedly increasing in size and thus requiring surgery are exceptional.

What Is the Outcome of Arachnoid Cysts?

Arachnoid cysts are incidentally discovered in 2.6% of the pediatric population and are more common in males;

in a large series of 309 arachnoid cysts, Al-Holou et al. [36] have reported that only 6.79% of the children underwent surgical treatment, including in most cases children presenting with progressive macrocephaly and hydrocephalus (11 children, aged from 1 week to 3 years 11 months) with a cyst located outside the posterior fossa.

Arachnoid cysts are usually sporadic. Arachnoid cysts of the posterior fossa are commonly diagnosed at prenatal imaging and information given to the parents has to be reassuring: the great majority of arachnoid cysts remains stable and does not require surgical treatment [37]. If the cyst interferes with the CSF circulation, due to its location, and if the patient is symptomatic, surgery is required: when possible, endoscopic fenestration is performed rather than extra- or intracranial shunting [38, 39] (fig. 8).

What Is the Outcome of DWM?

Despite many publications or studies about DWM, it remains difficult to give clear information regarding etiologies, clinical presentation, outcome and risk of recurrence. The main issue is the confusion in the literature until the early 2000s between DWM, vermian hypoplasia and the DW 'variant'. If we consider true DWM only, it has been reported to be associated with many chromosomal anomalies (30–50%) [40], genetic syndromes (Walker-Warburg syndrome) or with other brain malformations, in particular CCA [41]. When isolated, the DWM may be responsible for various clinical features: hydrocephaly, hypotonia, mental retardation, epilepsy;

cerebellar signs (ataxia, oculomotor apraxia) are less frequent than in Joubert syndrome; conversely, asymptomatic individuals have been reported [33]. This wide variability of phenotypes does not help prenatally when information has to be given to parents. Nevertheless, there is a consensus based on several studies [33] but mainly on Boddaert et al. [42] about neurodevelopmental outcome being normal when DWM is isolated and when the vermis is normally lobulated. More recently, Gandolfi Colleoni et al. [43] reported a good outcome in isolated DWM in only 50% of patients.

What Is the Risk of Recurrence?

It depends on the underlying pathology. True isolated DWM appears to be mainly sporadic [41], but recurrence in siblings has been reported and chromosomal anomalies have led to describe three DWM linked loci on chro-

mosomes 3, 6 and 7 [44]. Deletions or duplications of FOXC1, located on chromosome 6, are associated with cerebellar malformations including DWM, vermian hypoplasia, and megacisterna magna [45].

Conclusion

Prenatal neurocounseling is challenging and requires a good knowledge of the outcome of the different cerebral malformations. It is mainly based on an appropriate description of the cerebral anomaly; in some cases, a precise localization of the damage may have a prognostic impact. Therefore, the role of prenatal imaging is pivotal. However, the parents must be informed about the limitations of diagnostic accuracy.

References

- Melchiorre K, Bhide A, Gika AD, Pili G, Papageorgiou AT: Counseling in isolated mild fetal ventriculomegaly. *Ultrasound Obstet Gynecol* 2009;34:212–224.
- Dhouib A, Blondiaux E, Moutard ML, Billette de Villemeur T, Chalard F, Jouannic JM, Ducou le Pointe H, Garel C: Correlation between pre- and postnatal cerebral magnetic resonance imaging. *Ultrasound Obstet Gynecol* 2011;38:170–178.
- Glenn OA, Cuneo AA, Barkovich AJ, Hashemi Z, Bartha AL, Xu D: Malformations of cortical development: diagnostic accuracy of fetal MR imaging. *Radiology* 2012;263:843–855.
- Santo S, D'Antonio F, Homfray T, Rich P, Pili G, Bhide A, Thilaganathan B, Papageorgiou AT: Counseling in fetal medicine: agenesis of the corpus callosum. *Ultrasound Obstet Gynecol* 2012;40:513–521.
- Ghi T, Carletti A, Contro E, Cera E, Falco P, Tagliavini G, Michelacci L, Tani G, Youssef A, Bonasoni P, Rizzo N, Pelusi G, Pili G: Prenatal diagnosis and outcome of partial agenesis and hypoplasia of the corpus callosum. *Ultrasound Obstet Gynecol* 2010;35:35–41.
- Achiron R, Achiron A: Development of the human fetal corpus callosum: a high-resolution, cross-sectional sonographic study. *Ultrasound Obstet Gynecol* 2001;18:343–347.
- Blondiaux E, Garel C: Fetal cerebral imaging – ultrasound vs. MRI: an update. *Acta Radiol* 2013;54:1046–1054.
- Sotiriadis A, Makrydimas G: Neurodevelopment after prenatal diagnosis of isolated agenesis of the corpus callosum: an integrative review. *Am J Obstet Gynecol* 2012;206:337.e1–e5.
- Fratelli N, Papageorgiou AT, Prefumo F, Bakalis S, Homfray T, Thilaganathan B: Outcome of prenatally diagnosed agenesis of the corpus callosum. *Prenat Diagn* 2007;27:512–517.
- Mangione R, Fries N, Godard P, Capron C, Mirlesse V, Lacombe D, Duyme M: Neurodevelopmental outcome following prenatal diagnosis of an isolated anomaly of the corpus callosum. *Ultrasound Obstet Gynecol* 2011;37:290–295.
- Paul LK, Brown WS, Adolphs R, Tyszka JM, Richards LJ, Mukherjee P, Sherr EH: Agenesis of the corpus callosum: genetic, developmental and functional aspects of connectivity. *Nat Rev Neurosci* 2007;8:287–299.
- Moutard ML, Kieffer V, Feingold J, Lewin F, Baron JM, Adamsbaum C, Gelot A, Isapof A, Kieffer F, de Villemeur TB: Isolated corpus callosum agenesis: a ten-year follow-up after prenatal diagnosis (how are the children without corpus callosum at 10 years of age?). *Prenat Diagn* 2012;32:277–283.
- Goodyear PW, Bannister CM, Russell S, Rimmer S: Outcome in prenatally diagnosed fetal agenesis of the corpus callosum. *Fetal Diagn Ther* 2001;16:139–145.
- Volpe P, Paladini D, Resta M, Stanziano A, Salvatore M, Quarantelli M, De Robertis V, Buonadonna AL, Caruso G, Gentile M: Characteristics, associations and outcome of partial agenesis of the corpus callosum in the fetus. *Ultrasound Obstet Gynecol* 2006;27:509–516.
- Fuchs F, Moutard ML, Blin G, Sonigo P, Mandelbrot L: Prenatal and postnatal follow-up of a fetal interhemispheric arachnoid cyst with partial corpus callosum agenesis, asymmetric ventriculomegaly and localized polymicrogyria. Case report. *Fetal Diagn Ther* 2008;24:385–388.
- Li Y, Sansgiri RK, Estroff JA, Mehta TS, Pous-saint TY, Robertson RL, Robson CD, Feldman HA, Barnewolt C, Levine D: Outcome of fetuses with cerebral ventriculomegaly and septum pellucidum leaflet abnormalities. *AJR Am J Roentgenol* 2011;196:W83–W92.
- Bault JP, Salomon LJ, Guibaud L, Achiron R: Role of three-dimensional ultrasound measurement of the optic tract in fetuses with agenesis of the septum pellucidum. *Ultrasound Obstet Gynecol* 2011;37:570–575.
- Lepinard C, Coutant R, Boussion F, Loisel D, Delorme B, Biquad F, Bonneau D, Guichet A, Descamps P: Prenatal diagnosis of absence of the septum pellucidum associated with septo-optic dysplasia. *Ultrasound Obstet Gynecol* 2005;25:73–75.
- Damaj L, Bruneau B, Ferry M, Moutard ML, Garel C, Odent S, Adamsbaum C, Avni F, Tre-guier C, Lazaro L: Pediatric outcome of children with the prenatal diagnosis of isolated septal agenesis. *Prenat Diagn* 2010;30:1143–1150.
- Garcia-Arreza A, Garcia-Diaz L, Fajardo M, Carreto P, Antinolo G: Isolated absence of septum pellucidum: prenatal diagnosis and outcome. *Fetal Diagn Ther* 2013;33:130–132.
- Hehr U, Pineda-Alvarez DE, Uyanik G, Hu P, Zhou N, Hehr A, Schell-Apacik C, Altus C, Daumer-Haas C, Meiner A, Steuernagel P, Roessler E, Winkler J, Muenke M: Heterozygous mutations in SIX3 and SHH are associated with schizencephaly and further expand the clinical spectrum of holoprosencephaly. *Hum Genet* 2010;127:555–561.
- Dattani ML, Martinez-Barbera J, Thomas PQ, Brickman JM, Gupta R, Wales JK, Hindmarsh PC, Beddington RS, Robinson IC: Molecular genetics of septo-optic dysplasia. *Horm Res* 2000;53(suppl 1):26–33.

- 23 Garel C, Rosenblatt J, Moutard ML, Heron D, Gelot A, Gonzales M, Mine E, Jouannic JM: Fetal intracerebral hemorrhage and COL4A1 mutation: promise and uncertainty. *Ultrasound Obstet Gynecol* 2013;41:228–230.
- 24 Bilguvar K, DiLuna ML, Bizzarro MJ, Bayri Y, Schneider KC, Lifton RP, Gunel M, Ment LR: COL4A1 mutation in preterm intraventricular hemorrhage. *J Pediatr* 2009;155:743–745.
- 25 Elchalal U, Yagel S, Gomori JM, Porat S, Beni-Adani L, Yanai N, Nadjari M: Fetal intracranial hemorrhage (fetal stroke): does grade matter? *Ultrasound Obstet Gynecol* 2005;26:233–243.
- 26 Ghi T, Simonazzi G, Perolo A, Savelli L, Sandri F, Bernardi B, Santini D, Bovicelli L, Pilu G: Outcome of antenatally diagnosed intracranial hemorrhage: case series and review of the literature. *Ultrasound Obstet Gynecol* 2003;22:121–130.
- 27 Massoud M, Cagneaux M, Garel C, Varenne N, Moutard ML, Billette T, Benezit A, Rougeot C, Jouannic JM, Massardier J, Gaucherand P, Desportes V, Guibaud L: Prenatal unilateral cerebellar hypoplasia in a series of 26 cases: significance and implications for prenatal diagnosis. *Ultrasound Obstet Gynecol* 2013, Epub ahead of print.
- 28 Poretti A, Limperopoulos C, Roulet-Perez E, Wolf NI, Rauscher C, Prayer D, Muller A, Weissert M, Kotzaeridou U, Du Plessis AJ, Huisman TA, Boltshauser E: Outcome of severe unilateral cerebellar hypoplasia. *Dev Med Child Neurol* 2010;52:718–724.
- 29 Yoneda Y, Haginoya K, Kato M, Osaka H, Yokochi K, Arai H, Kakita A, Yamamoto T, Otsubuki Y, Shimizu S, Wada T, Koyama N, Mino Y, Kondo N, Takahashi S, Hirabayashi S, Takanashi J, Okumura A, Kumagai T, Hirai S, Nabetani M, Saitoh S, Hattori A, Yamasaki M, Kumakura A, Sugo Y, Nishiyama K, Miyatake S, Tsurusaki Y, Doi H, Miyake N, Matsumoto N, Saitsu H: Phenotypic spectrum of COL4A1 mutations: porencephaly to schizencephaly. *Ann Neurol* 2013;73:48–57.
- 30 Garel C: Posterior fossa malformations: main features and limits in prenatal diagnosis. *Pediatr Radiol* 2010;40:1038–1045.
- 31 Guibaud L, des Portes V: Plea for an anatomical approach to abnormalities of the posterior fossa in prenatal diagnosis. *Ultrasound Obstet Gynecol* 2006;27:477–481.
- 32 Long A, Moran P, Robson S: Outcome of fetal cerebral posterior fossa anomalies. *Prenat Diagn* 2006;26:707–710.
- 33 Bolduc ME, Limperopoulos C: Neurodevelopmental outcomes in children with cerebellar malformations: a systematic review. *Dev Med Child Neurol* 2009;51:256–267.
- 34 Forzano F, Mansour S, Ierullo A, Homfray T, Thilaganathan B: Posterior fossa malformation in fetuses: a report of 56 further cases and a review of the literature. *Prenat Diagn* 2007;27:495–501.
- 35 Heard AJ, Urato AC: The isolated mildly enlarged cisterna magna in the third trimester: much ado about nothing? *J Ultrasound Med* 2011;30:591–593.
- 36 Al-Holou WN, Yew AY, Boomsaad ZE, Garton HJ, Muraszko KM, Maher CO: Prevalence and natural history of arachnoid cysts in children. *J Neurosurg Pediatr* 2010;5:578–585.
- 37 Hayward R: Postnatal management and outcome for fetal-diagnosed intracerebral cystic masses and tumours. *Prenat Diagn* 2009;29:396–401.
- 38 Olaya JE, Ghostine M, Rowe M, Zouros A: Endoscopic fenestration of a cerebellopontine angle arachnoid cyst resulting in complete recovery from sensorineural hearing loss and facial nerve palsy. *J Neurosurg Pediatr* 2011;7:157–160.
- 39 Kurabe S, Sasaki O, Mitsunashi D, Koike T: Growing posterior fossa arachnoid cyst causing tonsillar herniation and hydrocephalus. *Arch Neurol* 2011;68:1606–1607.
- 40 Ecker JL, Shipp TD, Bromley B, Benacerraf B: The sonographic diagnosis of Dandy-Walker and Dandy-Walker variant: associated findings and outcomes. *Prenat Diagn* 2000;20:328–332.
- 41 Parisi MA, Dobyns WB: Human malformations of the midbrain and hindbrain: review and proposed classification scheme. *Mol Genet Metab* 2003;80:36–53.
- 42 Boddaert N, Klein O, Ferguson N, Sonigo P, Parisot D, Hertz-Pannier L, Baraton J, Emond S, Simon I, Chigot V, Schmit P, Pierre-Kahn A, Brunelle F: Intellectual prognosis of the Dandy-Walker malformation in children: the importance of vermian lobulation. *Neuroradiology* 2003;45:320–324.
- 43 Gandolfi Colleoni G, Contro E, Carletti A, Ghi T, Campobasso G, Rembouskos G, Volpe G, Pilu G, Volpe P: Prenatal diagnosis and outcome of fetal posterior fossa fluid collections. *Ultrasound Obstet Gynecol* 2012;39:625–631.
- 44 Liao C, Fu F, Li R, Yang X, Xu Q, Li DZ: Prenatal diagnosis and molecular characterization of a novel locus for Dandy-Walker malformation on chromosome 7p21.3. *Eur J Med Genet* 2012;55:472–475.
- 45 Aldinger KA, Lehmann OJ, Hudgins L, Chizhikov VV, Bassuk AG, Ades LC, Krantz ID, Dobyns WB, Millen KJ: FOXC1 is required for normal cerebellar development and is a major contributor to chromosome 6p25.3 Dandy-Walker malformation. *Nat Genet* 2009;41:1037–1042.