ORIGINAL ARTICLE

Fetal magnetic resonance imaging in midline malformations of the central nervous system and review of the literature

IRM fœtale dans les malformations de la ligne médiane du système nerveux central et revue de la littérature

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Summary Fetal magnetic resonance imaging (MRI) is a well-established second line imaging modality in identifying complex pathologies of the central nervous system (CNS), especially when ultrasound (US) findings are equivocal. It may enable an early and precise diagnosis, which is essential in terms of management of pregnancy and pre-, peri- and postnatal care. We present three cases with rare complex midline malformations of the CNS, diagnosed prenatally by fetal MRI. Two cases revealed holoprosencephaly; one case demonstrated rhombencephalosynapsis. In addition, we reviewed the literature and provide a summary of recent findings regarding cerebral midline development and discuss the advantages of fetal MRI.

Introduction
Prenatal ultrasound (US) examination is a standard and effective screening method in detecting pathologies of the fetal central nervous system (CNS). When US findings are equivocal, fetal magnetic resonance imaging (MRI) is a powerful second-line imaging tool to study and identify complex abnormalities of the CNS enhancing accuracy and specificity of diagnosis.

Since fetal MRI is not (yet) widely available, there are only few reports regarding prenatal MRI diagnosis of complex malformations of the CNS [1–5]. Familiarity with
the prenatal MRI findings is essential to recognize cerebral pathologies accurately and prospectively. We present MRI findings in three fetuses with complex midline malformations. All fetuses were referred because of suspected CNS malformations as seen on prenatal US. Fetal MRI confirmed semilobar holoprosencephaly (HPE) in two fetuses and rhombencephalosynapsis (RES) in one fetus. The goal of our case report is (a) to present the fetal MRI findings of HPE and RES, (b) to discuss the value of fetal MRI in the early diagnoses of these malformations and (c) to summarize the current main stream literature concerning the etiology of HPE and RES.

Case reports

Case 1

A 38-year-old woman, gravida 2 para 2 (G2P2) was referred to our institution because of an abnormal prenatal US at 23 weeks’ gestational age (GA). Her first pregnancy was uneventful with delivery of a term baby girl. During the second pregnancy, US, which was performed as part of the routine prenatal screening, had revealed a significant hydrocephalus most likely as part of a semilobar holoprosencephaly malformation complex. Clinically, the pregnancy was experienced as unremarkable by the mother. Subsequent fetal MRI confirmed semilobar holoprosencephaly with a single lobed forebrain, fused deep gray nuclei, absent septum pellucidum, partial development of the occipital and temporal horns, a hypoplastic posterior corpus callosum and a hypoplastic posterior falx cerebri (Fig. 1). In addition, a mild hypotelorism in combination with a situs inversus totalis was diagnosed. Amniocentesis revealed a female karyotype consistent with trisomy 18. Because of the inauspicious prognosis, the parents decided to terminate pregnancy. Autopsy was refused by the parents.

Case 2

A 25-year-old woman, G2P2, presented at 23 weeks’ GA at our institution after a routine prenatal US, suspected semilobar holoprosencephaly, microcephaly and a cleft lip/palate deformity. The mother had not experienced anything wrong during this pregnancy. The first pregnancy was uneventful with term delivery of a healthy baby girl. Fetal MRI performed on the same day, confirmed US diagnosis, however the higher spatial resolution and contrast-to-noise ratio of fetal MRI allowed correcting diagnosis to alobar holoprosencephaly with a monoventricle and fusion of forebrain, thalami, and basal ganglia (Fig. 2). The karyotype from amniocentesis was 46XX 15ps+, resembling a normal variant. The parents decided to terminate pregnancy at 26 weeks’ GA.

Case 3

A 34-year-old woman, G2P2, was referred to our institution because of an abnormal prenatal US at 31 weeks’ GA which had revealed mild hydrocephalus, absent corpus callosum, hypoplastic cerebellum, polyhydramnios and a mildly dilated right renal pelvis. Only one umbilical artery was noted. Clinically, the mother experienced the pregnancy as unremarkable. The first pregnancy was uneventful, a healthy term baby boy was born. Fetal MRI was performed at 32 weeks’ GA to determine the exact etiology of the hydrocephalus. Fetal MRI confirmed mild hydrocephalus associated with a small, single lobed cerebellum with absent cerebellar vermis compatible with classical rhombencephalosynapsis (Fig. 3). The corpus callosum was intact but thinned by the hydrocephalus, the septum pellucidum was partially ruptured. The interthalamic adhesion appeared prominent. Polyhydramnios was confirmed, the esophagus did not appear dilated, the stomach was filled with fluid. An esophageal atresia could not be diagnosed for

Figure 1  Axial (A) and sagittal/coronal (B) T2-weighted single-shot fast spin-echo MRI in the 23 weeks of gestation (patient 1). Semilobar holoprosencephaly with a single lobed forebrain, fused central gray matter, absent septum pellucidum, partial development of the occipital and temporal horns and a hypoplastic posterior falx cerebri.
Alobar holoprosencephaly with a monoventricle and fusion of thalami and basal ganglia. No posterior falx cerebri visible.

Rhombencephalosynapsis with a single lobed cerebellum and a mild hydrocephalus. Partially ruptured septum pellucidum and fused thalami. A two-vessel umbilical cord is seen (arrow). Fluid is apparent within the proximal esophagus as well as within the stomach.

certainty. The umbilical cord showed a two-vessel architecture. A female infant was born at 38 weeks’ GA via caesarian section. Postnatally, esophageal atresia type IIIb was established as the cause of the polyhydramnios. Postnatal MRI confirmed RES with mild ventriculomegaly, absent septum pellucidum and fused thalami. Because of her complex brain malformation, poor neurodevelopmental prognosis and the need for extensive surgical intervention (to correct the esophageal atresia) the parents choose a regime of comfort care. The infant died on the third day post partum. Postmortem evaluation and review of photos established the final diagnosis of Gomez Lopez Hernandez syndrome (GLHS). Inspection of the child had shown bilateral alopecia, low-set, posteriorly rotated ears, hypertelorism, narrow palpebral fissures, smooth philtrum and thin lips. Chromosomal analysis of a postmortem skin biopsy revealed a normal female karyotype (46,XX).

All fetal MRI were performed using a 1.5 Tesla MRI unit machine using standard departmental protocols as have been published previously. Imaging included multiplanar T2 weighted single shot fast spin-echo sequences covering the entire fetus using the cardiac phased array surface coil [6].

Discussion

Fetal MRI has become a well-established second line imaging modality to examine the fetus intrauterine, especially if a complex cerebral pathology is suspected. The diagnostic value of prenatal US is limited in the exact evaluation of the fetal brain: [1,7,8]:

- The acoustic shadowing of the fetal skull does not allow a detailed study of the cerebral cortex, regarding progressing of neuronal migration and advancing myelination of the white matter.
- Accurate evaluation of the posterior fossa including brainstem and cerebellum is limited.
- The maternal pelvic bones may obscure anatomical details of the fetal brain, especially towards the end of the pregnancy when the fetal head is descending into the small pelvis.
- Subtle anatomical abnormalities of the fetal brain may go undetected by US.
- Finally, maternal body habitus, maternal bowel gas and a low amount of amniotic fluid may further limit US.

The need for an alternative imaging modality is straightforward [3,9]. Fetal MRI has proven to be an important secondary imaging modality to confirm, correct or complete US diagnosis [1—5]. Frequently, the most obvious findings are only the “top of the iceberg”. Identification of the exact extent of fetal pathology is important to estimate future prognosis, to guide pre-, peri- and postnatal treatment, to determine the best mode of delivery and may also be essential to counsel parents for future pregnancies [1—3,5,10].

Ventriculomegaly is one of the most frequent indications for fetal MRI, with the underlying cause being highly variable. Imaging should differentiate between (a) isolated ventriculomegaly caused by congenital aqueductal stenosis, (b) secondary ventriculomegaly, due to intracerebral/intraventricular hemorrhage, and (c) syndromal ventriculomegaly as part of a complex cerebral malfor-
mation. Additional findings, like migrational abnormalities, schizencephaly or as in our cases, HPE or RES may only be diagnosed incompletely or even go undetected by US. However, identification of these additional findings is essential in terms of neonatal prognosis and treatment options. All of our cases presented with ventriculomegaly as a leading imaging finding on US examination. Fetal MRI was performed to determine the exact etiology of the ventriculomegaly and to rule out additional lesions.

Cases 1 and 2 HPE was detected in prenatal US, but the type of HPE could not be determined. Previous data show consistent experience with difficulties classifying HPE in US precisely. In a retrospective study with 104 patients diagnosed with holoprosencephaly, a low sensitivity of US, especially in detecting milder forms of HPE has been reported. Although 93% of these patients underwent US, a prenatal diagnosis of HPE was made in only 22% [11]. The higher spatial resolution and excellent contrast-to-noise ratio of fetal MRI easily allowed definite classification of HPE, ruling out additional CNS lesions, and providing extra information for a more reliable prediction of neurocognitive development and well-directed counseling of the parents.

HPE is a complex congenital brain malformation resulting from incomplete cleavage of the prosencephalon into right and left hemispheres, occurring between the 18th and 28th day of gestation. In this period, the prechordal plate mesoderm induces formation of ventral brain structures with bilateral subdivision. A complex signaling pathway with sonic hedgehog (SHH) as the major gene expressed in the ventral midline is essential for this process [12—19]. HPE is the most common developmental defect of the forebrain and midface in humans. The prevalence during early embryogenesis is 1 in 250 [20]. Only 3% of fetuses with HPE survive to delivery [21], resulting in a live birth prevalence of approximately 1 in 10,000 [22,23]. Though, the true prevalence may be underestimated, since advances in neuroimaging with MRI allow identification of milder forms, which have gone undiagnosed in the past.

There are three types of classic HPE:

- lobar:
  - right and left ventricles are separated;

- semilobar:
  - ventricles are partially separated;

- alobar:
  - ventricles fuse to form a monoventricle [24,25].

The sex ratio in alobar HPE has a 3:1 female predilection. Accordingly, both of our cases were female. In addition, a forth, milder subtype called middle interhemispheric variant, also known as syntelencephaly, involves the posterior frontal and parietal lobes and is presumed to have a different embryological derivation [13,26,27].

In most cases, midline craniofacial anomalies are associated in HPE, and there seems to be a correlation between the severity of facial dysmorphism with the underlying cerebral pathology in up to 80%, well-described as “the face predicts the brain” [28]. The facial characteristics are highly variable, ranging from cyclopia, ethmocephaly, cebrocephaly to ocular hypotelorism, single central incisor, anosmia, cleft lip and flat nose [14,24]. In summary, HPE presents a continuous spectrum of midline cerebral and craniofacial anomalies, revealing severe forms with alobar HPE and cyclopia on one end, and microforms with normal brain anatomy in MRI and only mild facial anomalies on the other end [14,16,17].

The etiology of HPE is heterogeneous, believed to be of multigenetic and multihit origin to account for the extreme clinical variability [29]. However, the majority of HPE cases seem to be sporadic. HPE is often associated with chromosomal anomalies, with some authors reporting anomalies in 41 to 57% of cases [22,30—32]. This matches our finding of a trisomy 18 karyotype in patient 1. In the literature, it appears that trisomy 13 has an intimate relationship with HPE; as many as half of all cases with HPE have abnormal karyotypes [22,30]. Furthermore, 70% of patients with trisomy 13 have HPE [33,34]. However, there are no conclusive data about the incidence of HPE in trisomy 18; only one case series found that 1 of 49 patients with trisomy 18 had HPE [35]. Other reports did not specifically describe HPE in their series, although other intracerebral pathologies including choroid plexus cysts, ventriculomegaly, Dandy-Walker-malformation, and anomaly of the posterior fossa were observed [36—38]. Extracranial anomalies like cardiac and limb malformations are very common in trisomy 18 [35—38], though a situs inversus as seen in our patient has not been mentioned previously.

In addition, HPE can manifest as part of a monogenic syndrome [22,30], such as Smith-Lemli-Opitz, CHARGE association, Pallister-Hall, Meckel syndrome, or velocardiofacial syndrome [22,30,33,39] with an incidence of HPE in up to 25% [22,30].

Finally, there are familial cases of non syndromic HPE as a solitary manifestation with normal karyotype, providing evidence for a genetic basis of HPE. Autosomal dominant, recessive, and possibly X-linked inheritance pattern have been reported [17,18,40]. Candidate genes responsible for such cases have been identified in at least 12 genomic regions [13,41]. SHH is the major gene implicated in the pathogenesis of HPE [18,41,42]. Its protein plays an essential role in the induction and differentiation of the ventral parts of the neural tube [43]. Besides SHH, there are other genes involved in the SHH-signaling pathway, including PATCHED1 (PTCH), TGFIF, PTC1, TDGF1, ZIC2, SIX3, GL12, FGF8, and FAST1 [13,16,19,29,41]. It has been shown, that heterozygous mutations in two HPE genes such as SHH and TGFIF [18], SHH and ZIC2 [18], and PTC1 and GL12 [40] result in a more severe phenotype. However, the pathogenesis and molecular regulation of the midline craniofacial anomalies are unknown. In familial HPE, striking clinical variability in a single pedigree has been observed [42]. Among carriers of the abnormal gene, there are individuals presenting with the full range of HPE, microforms or even no clinical abnormalities [33,44]. Based on analysis of autosomal dominant pedigrees, the estimated frequency is 37% for HPE, 27% for microforms, and remarkably 36% for phenotypically normal individuals [33]. Thus, normal carriers are at risk of having children with HPE.

Although it seems likely, that multiple genes determine the phenotype of HPE, animal and human models have shown an additional influence of environmental factors, such as maternal diabetes mellitus or gestational diabetes, alco-
holism, cigarette smoking, prenatal exposure to drugs such as antiepileptica and retinoic acid, and prenatal infections such as intrauterine cytomegalovirus infection [29,45]. It is believed, that two or more events involving genes and/or environmental factors contribute to HPE. In our second case with alobar HPE and cleft lip/palate without other anomalies, the etiology is difficult to determine, since both familial cause and sporadic occurrence is possible.

Genetic counseling of the parents regarding HPE is a challenge, because of the complexity of many contributing factors, some of which are unpredictable or still unknown, and a high risk of recurrence in up to 13% in apparently sporadic cases [46]. Patients with HPE may face many medical problems including developmental delay, epilepsy, hypotonia, spasticity, dystonia, endocrine disorders, craniofacial malformations, oculomotor disorders, and autonomic dysfunction [14,17,47]. There is a correlation between severity of craniofacial malformations/type of HPE and clinical outcome. With cyclopia, ethmocephaly, or cebocephaly, virtually all patients die within the first week, with median cleft lip 50% survive for four to five months [46]. Patients with semilobar and lobar HPE tend to have better survival rates than patients with alobar HPE, some of them living well into adulthood [29,46]. Since milder forms of HPE can be detected by MRI, more and more patients can be identified now. These patients may reveal mild to moderate mental retardation or may even have normal intelligence [46,47]. The wide spectrum of outcomes emphasizes the importance of precise neuroradiological classification of HPE.

Case 3 is a patient with RES. This rare disorder was first described by Heinrich Obersteiner from Vienna 1914 as an incidental autopsy finding in a patient without previous cerebellar symptoms [48]. In the last decade, RES has been increasingly recognized in vivo as MRI became more available and posterior fossa malformations could be better visualized. However, there are only few reports regarding prenatal diagnosis of RES [49—51].

Similar to HPE, an early, correct and complete identification of RES is essential to guide pregnancy, to estimate fetal prognosis and to counsel parents. In our patient, the leading findings on prenatal US were hydrocephalus and corpus callosum agenesis. The cerebellar malformation resembling RES could only be identified by fetal MRI. This piece of information is essential to predict fetal outcome and prognosis. US is typically limited in interpreting the fetal posterior fossa. Artifacts and acoustic shadowing by the skull base prevent a detailed anatomical evaluation of the cerebellum and brainstem. In addition, in our case fetal MRI allowed differentiation between agenesis of the corpus callosum and a significant thinning of the corpus callosum due to the hydrocephalus. Again, the hydrocephalus was the leading sign and served as the "tip of the iceberg". Unfortunately, the postnatally diagnosed esophageal atresia, was missed by both US and fetal MRI. Even on retrospective analysis, the esophageal atresia could not be identified for certainty on fetal MRI. It should however be mentioned that the fetal MRI was focused on the fetal CNS.

Key features of RES are agenesis or hypogenesis of the vermis, dorsal fusion of the cerebellar hemispheres, and fusion of the superior cerebellar peduncles and dentate nuclei, which arch in a horseshoe shape across the midline, resulting in a misshapen fourth ventricle mostly described as the shape of a keyhole, diamond, tear drop, or square on axial MRI images [52—55]. The diagnosis is best confirmed on coronal MRI revealing an abnormal horizontal orientation of the cerebellar folia [52].

The frequency of RES in the pediatric population is estimated to be approximately 0.13% [56].

RES seems to be a sporadic disorder [52,56], without familial recurrence, though there are cases of children born to consanguineous parents, proposing an autosomal recessive inheritance [57—59]. One case has been reported with an interstitial deletion of 2q [60]. It is uncertain, whether teratogenic factors contribute to the pathogenesis of RES. There have been single cases of RES occurring after maternal sodium valproate and clonazepam therapy [59], ethosuximide medication [61] and phencyclidine abuse [62].

RES is thought to result from a disturbed cerebellar development between 28 and 41 days of gestation [52]. The precise mechanism of embryologic cerebellar development is not fully understood. In the traditional view, the cerebellum arises from two distinct embryonic primordia, known as the rhombic lips, with the vermis developing superiorly between these structures [63]. This concept however cannot explain the genesis of RES. Another more recent view, proposes a primary unpaired cerebellar primordium [64]. According to this theory, RES results from failure in vermian differentiation, leaving the cerebellar hemispheres fused [53]. Experimental studies have identified the "isthmic organizer", a band of neuroepithelium at the border between metencephalon (the area from which the cerebellar hemispheres derive) and mesencephalon (the area from which the vermis partly derives) [65—67], which is assumed to be crucial for cerebellar development. RES is likely to be caused by a genetic deficit in the isthmic organizer, resulting in abnormal cerebellar patterning [67]. Several genes have shown to be involved in this genetic pathway: En1, En2, Pax2, Lmx1a, Lmx1b, FGF8, and Wnt1 [68—71]. One candidate molecule has been identified in the mutant mouse Dreher, which has a homozygous mutation of Lmx1a resulting in agenesis of the vermis and fusion of the cerebellar hemispheres, closely resembling human RES [72].

Additional, supratentorial midline abnormalities are common in patients with RES, the most frequent being ventriculomegaly secondary to aqueductal stenosis, dysgenesis of the corpus callosum, and agenesis of the septum pellucidum [49,52,56,58,59,61,73,74]. Other associated anomalies include variable fusion of the thalami, tectum and fornices, hypoplasia of the anterior commissure and optic chiasm, underdevelopment of the temporal lobes, malformations of the pituitary gland, agenesis of the olfactory bulbs/tracts, and subcortical and/or periventricular heterotopias [49,52,56,59,73,75—77]. Interestingly, two cases have been reported in association with Chiari II malformation and meningocele, suggesting a new anomaly of hindbrain and spine [78,79]. One unique case presented telencephalosynapsis together with RES and a posterior fossa ventriculocoele as an aberrant syngenic CNS phenotype [80]. No further cerebral pathology was found in our case. Extracranial anomalies have previously been described including respiratory, genitourinary, and frequently, musculoskeletal abnormalities [49,59,73,81,82]. Gastrointestinal abnormalities are rarely present, only one recently
described case showed duodenal atresia [49]. Our patient showed however an esophageal atresia type IIIb. Further postnatal analysis also showed hypertelorism, palpebral fissures, a smooth philtrum, thin lips, posteriorly rotated, low-set ears and a parietal alopecia refining the final diagnosis into a Gomez-Lopez-Hernandez syndrome (GLHS) or cerebello-trigeminal-dermal dysplasia [83,84]. The postnatal findings of patient 3 have been published previously summarizing the clinical findings in a series of four patients with GLHS [85]. Thus, RES can be found as an isolated finding or as part of a complex malformation syndrome as seen in our patient. GLHS is a very rare entity with only approximately 20 cases described thus far. It is characterized by the triad of RES, parietal alopecia, and trigeminal anesthesia [51,83,84,86,87]. Usually, the diagnosis can only be made postnatally when bilateral alopecia becomes evident or trigeminal anesthesia is noted. There is no evidence that GLHS is associated with other malformations [86,87], separating the esophageal atresia in our case into a distinct entity. The prognosis of this condition is still unclear, with reports presenting both poor and favorable outcome [86].

Patients with RES present with a broad range of symptoms, including seizure disorder, ataxia, spasticity, hypotonia, involuntary head movements, and abnormal eye movements, many of which range from mild to debilitating, depending on the severity of other associated pathologies [49,52,54,58,74,75]. Also, the cognitive development is markedly variable ranging from severely handicapped to normal [58,59,88,89]. Behavioral and psychiatric problems, such as obsessive compulsive disorder, self mutilation, suicidality and depression have been observed in association with RES [48,56,88,90–92]. A high frequency of attention problems has been recently described in a case series [89], proposing an organic correlate, since the vermis is thought to play an important role in the cerebellar-thalamo-prefrontal circuit. This pathway controls inhibition, motor, and executive function and may be disturbed in RES patients due to an absent vermis.

The outcome of RES is not conclusively predictable, since there are patients who die in childhood due to severe disabilities [49], and others who grow into adulthood with either subtle or nonexistent clinical signs, the diagnosis of RES being made incidentally [48,49,73,74,88,90,93,94]. The prognosis likely depends on the severity of associated pathologies, particularly supratentorial anomalies and hydrocephalus [49,91]. However, there are no reliable data available supporting this hypothesis due to the paucity of case reports and lack of long-term data available as RES is both rare and a relatively newly recognized condition.

Fetal MRI has provided remarkable insights into fetal brain anatomy, enabling in many cases a precise diagnosis and classification of complex cerebral malformations earlier in pregnancy. Several studies have investigated the advantages/disadvantages of fetal MRI compared to US in regards to diagnosis, parental counseling, and management in patients with suspected intracranial pathologies. It has been shown that MRI changed the diagnosis in 28–48%, counseling in 39–50%, and management in 19–46% of all cases [1–4,6,95–98]), establishing fetal MRI as being crucial for classification of malformations in utero. The distinction between syndromal and sporadic type of complex brain anomalies is critical, as they may have completely different prognoses. This information is crucial for adequate counseling of parents during this emotionally labile period of pregnancy. An early diagnosis aids parents by establishing expectations and securing additional time needed to make an appropriate decision concerning the continuation of their pregnancy and pre-, peri- and postnatal care.

The presented cases underline the significance of fetal MRI in the complete diagnosis of complex midline malformations of the brain. The additional findings revealed by fetal MRI and the increased accuracy of the diagnosis strengthened and guided the decision making related to pre-, peri- and postnatal management as well as the counseling of pregnancy. The higher spatial resolution and high contrast to noise ratio allowed a precise, reliable diagnosis. In addition, fetal MRI reinforced diagnosis by confirming questionable or correcting incomplete US findings. The most obvious findings, like hydrocephalus as part of a holoprosencephaly complex were correctly suspected by prenatal US. Fetal MRI allowed making the correct classification. Moreover, in the third case, fetal MRI identified the absence of the cerebellar vermis which was not recognized on prenatal US.

Conclusion

Complex cerebral midline defects like HPE and RES can be reliably diagnosed today with the advent of fetal MRI. While there are valid data concerning prognosis and outcome of HPE, counseling regarding RES is rather difficult because of the limited number of case reports and long-term data.

More advanced methods, such as MRI with higher resolution, MR-spectroscopy, or diffusion tensor imaging, may provide further information regarding cerebral metabolism and pathology that may open new avenues of research and potential treatment modalities in the future.

The fetal radiologist should be familiar with the complexity of CNS malformations. It is a given rule that any physician is tempted to recognize predominantly those lesions that he is familiar with. Consequently, every fetal radiologist should be familiar with rare findings and should have a critical mass or number of fetal MRI examinations.

References


