MRI of the fetal nervous system: technical advances

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1. INTRODUCTION

Ultrasonography (US) is currently the primary imaging method for routine examination of the fetal brain1-4. However magnetic resonance imaging (MRI) provides a highly accurate depiction of the morphological changes of development in the normal brain5-14 and in fetal brain disorders8,15-25. Thus, MR imaging can often provide useful information when ultrasonography (US) is inconclusive. MR can provide improved anatomical resolution when US is limited by patient size, fetal presentation, or oligohydramnios. Another advantage to MR is that intracranial brain imaging is not impacted by calvarium, which allows clear identification of the cortex and subarachnoid space5. Fetal MRI has widely spread because of the development in fast imaging, and of the established safety of fetal MRI. MRI can be performed several times during the course of pregnancy, which permits the documentation of the natural history of brain injury over gestational age20. MR imaging, which is also an excellent alternative to autopsy, may be a valuable adjunct to autopsy for fetuses with central nervous system (CNS) anomalies26,27. Optimal MR imaging technique is necessary in order to collect as much information as possible about the fetal brain condition20. Aside conventional sequences, diffusion images can also be
used routinely \(^{28-30}\). Monovoxel proton spectroscopy can also be performed in utero, but this technique is being used in research protocols and is not yet employed in a routine clinical protocol.

2. TECHNIQUES FOR FETAL BRAIN INVESTIGATION

MRI is usually performed in vivo during the second half of gestation (from 18 weeks on), because ultrasound can usually accurately diagnose brain abnormalities before week 18-20. Below 18 weeks of gestation, MRI resolution is typically poor due to a thin cerebral mantle and relatively enlarged ventricles, which prevents detection of subtle changes within the cortical ribbon and the white matter. \(^{5}\)

Technical considerations are largely reported in the literature \(^{9,10,14,20,31}\). Images are obtained routinely in sagittal, coronal and axial planes relative to the fetal head with both T1 and T2 weighted sequences. A combination of phased array coils currently is used with a magnet of 1.5 Tesla, which results in good signal homogeneity.

Optimal imaging parameters have to be adapted to the brain composition, especially the T2 weighted images (WI) because MR images obtained at different stages of development have changes due to alterations in brain tissue water content (mainly within the white matter), multiplication of glial cells which precedes myelination (the so-called myelination gliosis), and accumulation of intracellular lipid myelin precursors, particularly galactocerebrosides. T2 weighted Turbo Spin Echo (TSE) sequences have been a very good compromise with an acceptable acquisition time (from 2 to 3 min). T2- weighted single-shot sequences such as HASTE (Half-Fourier Single Shot Turbo Spin–Echo), which provides heavily T2 weighted images in only seconds, are currently performed to “freeze” the fetus because of sequential slice capability; those images, which require a magnet of high gradient strength, are acquired much more quickly than TSE images (about 2 s for each slice that is 30 s for 15 slices) and are true T2 weighted images with low susceptibility weighting. HASTE images with a high matrix of 512 may be also obtained and give excellent identification of the layering of the cerebral parenchyma and low chemical shift artifacts compared to HASTE images with lower matrix of 256. \(^{20}\) T2 WI of TRUE FISP type can also be performed. However the contrast obtained in the brain is not as clear as with HASTE images. On the other hand, TRUE FISP images are highly accurate in evaluating the face and skull base, in depicting old hemorrhage, calcifications, as well as lipomas.
in young fetuses. Thin sections of 1.5 mm can be achieved with 3D T2 WI, which are mainly used in the evaluation of the midline (partial corpus callosum agenesis, aqueduct stenosis). MRI also requires T1 weighted images in order to look for normal transitory brain layering, the signal changes from the myelination process as well as to detect hemorrhage, leukomalacia, venous thrombosis, necrosis, calcifications, and abnormal bright signals from lipoma, and subependymal nodules of tuberous sclerosis. We use gradient echo images (FLASH sequence i.e. Fast Low Angle Shot) because of excellent differentiation between the cortical ribbon, the white matter, and the ventricular walls as opposed to TSE images. Lack of brain layering, which is normally seen in young fetuses (20-28 weeks of gestation), suggests cortical and/or white matter abnormalities.

Angiographic images can also be obtained on a 1.5 Tesla magnet when evaluating vascular malformation through a sequential 2D FLASH sequence that allows a good compromise between vascular and tissue contrast and permits Maximum Intensity Projection (MIP) reconstructions. Diffusion images (echo planar images) can also be performed such as in the neonatal period to detect cytotoxic and/or vasogenic edema through anisotropic, trace, and ADC images obtained with three b values (0, 500, 1000). However the acute response of the fetal brain is not as common as in the neonatal brain. T2 diffusion images (b value of 0) are extremely useful in detecting old and small hemorrhagic foci as well as calcifications. Diffusion images also have the capacity to show the normal maturation, especially the intermediate layer of the white matter prior 30 weeks of gestation, and the premyelinating tracts of the white matter in which signal changes are seen on diffusion images before conventional T1 and T2 sequences. Minor abnormalities of the corpus callosum in utero, as well as white matter anomalies, may be well identified on diffusion images.

3. TECHNICAL LIMITATIONS

Compared to the postnatal period, there is no coil devoted to the brain in utero with expected loss of signal. However technical tricks such as the use of phased array coils, technique of parallel acquisition and movement synchronization help improving the signal. No high-resolution T1 WI (e.g., 3D acquisition of 1mm thick sections with a matrix of 256 or 512) can be performed in utero so that small foci of malformation of the cortex such as polymicrogyria may be missed. The lack of a CSF flow sequence prevents complete evaluation of hydrocephalus or cystic
malformations. Gadolinium injections are not generally used in utero, which impedes identification of abnormal blood vessels.

4. INDICATIONS OF FETAL BRAIN MRI

MRI is usually performed because of abnormal US findings: Ventricular dilatation is the most frequent indication (40% of cases) followed by suspicion of a central nervous system (CNS) malformation (31% of cases) or brain injury\textsuperscript{8-10}. Obviously those conditions can overlap since an increased ventricular size may result from destruction, malformation, hydrocephalus, destruction and hydrocephalus, malformation and destruction. MRI is extremely helpful in the evaluation of ventriculomegaly because, compared to US, it has greater sensitivity in the detection of associated brain lesions\textsuperscript{32}.

MRI is commonly performed after a normal brain ultrasound within the following contexts: 1) familial (suspected familial disorder such as, tuberous sclerosis, neurofibromatosis type 1); 2) maternal (acute gestational/maternal event, infections, coagulation disorders); 3) fetal [twin pregnancy, fetuses presenting with extracerebral multiple malformations (e.g., thoracic lymphangioma and megalencephaly, cardiac malformation and leukomalacia) that can be associated with brain lesions].

MRI is not usually indicated in cases of intrauterine growth restriction (IUGR). However, it can provide useful information when IUGR is associated with progressive microcephaly or other abnormalities, such as fetal hydrops or arthrogryposis.

Ideally, MRI is performed at a neuroradiological unit at a tertiary care facility after US performed by a dedicated neurosonographer\textsuperscript{33}. Because intracranial anomalies can be missed in the second trimester, MRI is optimally performed in the late-second or third trimester\textsuperscript{34}.

5. GENERAL RULES OF BRAIN MRI IN UTERO

Anatomical and maturational effects on the MR signal change with gestational age, which correspondingly alters the pathological features detected by MRI. Thus, an inconclusive MR examination should be repeated, showing the natural history of a pathologic disorder. Moreover, the image itself may be confusing especially in young fetuses at 20 to 25 weeks of gestation: indeed different causes can display similar images.
6. ADVANCES TECHNIQUES

Kok et al. 35,36 have demonstrated the possibility of investigating in vivo the human fetal brain using 1H MRS with two MRS acquisition sequences: a stimulated echo acquisition mode (STEAM) with a short time of echo (TE) of 20 ms, and point-resolved spectroscopy (PRESS) with a long TE of 135 ms. Brain maturation has been associated 37 with significant increases in NAA (N-acetyl-aspartate), Glx (glutamine-glutamate), tCr (total creatine) and reduction of myo-inositol and lactate among other metabolites, based on ex utero studies. In our institution, PRESS sequences are used for both short- and long-echo time and brain development is characterized by a reduction in choline and myo-inositol, a rise NAA and creatine in conjunction with an increase in gestational age 38,39. No specific metabolic pattern has been identified in the different groups of brain abnormalities encountered in utero, although some characterization can be made 38. Increase in Cr may be seen in white matter gliosis that is not currently identified on conventional sequences. Hypoxic-ischemic pattern can be identified in twin-to-twin-transfusion syndrome and IUGR, as well as in complex malformation. The detection of an abnormal peak in association with a brain malformation can be suspicious for an inborn error of metabolism.

Diffusion study showed that the brainstem and cerebellar hemisphere, as well as the thalamus, undergo early maturation and myelination, with a strong linear negative age-related correlation of their ADC values 29,30. In the hemispheric white matter, a primary rise of ADC values is seen before the 30th GW in most deep white matter areas: this could be attributable to the cellular structure and transient nature of the intermediate zone containing migrating cells. The decrease of the ADC values afterwards, is the result of the disappearance of this intermediate zone in combination with other sequences of events that are already known to occur, especially the decrease in water content and the beginning of higher-order maturation including myelination. Diffusion tensor imaging (DTI) can also be performed in utero 40. Normal brain maturation is characterized by increase in FA (fraction of anisotropy) with decrease in ADC values between 31 and 37 weeks in some cerebral structures, especially the pyramidal tracts and the corpus callosum.

6. NORMAL DEVELOPING FETAL BRAIN ANATOMY

Morphological and signal changes of the developing brain have been illustrated in several
textbooks. Morphological changes consist of changes in ventricular shape, decrease in thickness of the germinal matrix, decrease in volume of the subarachnoid spaces, and the developing sulcus formation. Dramatic changes in sulcation can be seen by 24, 28-30, and 34-35 weeks of gestation, the time at which the gyration appears almost completely. Subarachnoid spaces can remain large throughout pregnancy particularly in the posterior areas (parieto-occipital) because of the evolving process of cavitation of the meninx primitiva. The maturation process is revealed by signal changes caused by high cellular density, myelination gliosis, and the formation of myelin proper. Dramatic changes can be seen as early as 20 weeks of gestation within the brainstem, germinal matrix, and white matter in which the intermediate layer of migrating cells is present until 30 weeks. Signal changes are also identified by week 33 within the posterior limb of the internal capsule and the optic tracts, and by 35 weeks within the centrum semi ovale as a consequence of the myelinated projecting fibers of the central area. The typical multilayered pattern constitutes an important normal hallmark, because its absence is highly suggestive of a white matter lesion. Anatomy and development of the human cerebellum is complex and MRI is able to show the appearance of the fissures of the cerebellum.

7. DETECTION OF FETAL BRAIN ANOMALIES
Brain malformations are characterized by their specific morphological changes, whereas brain injury displays abnormal signal, irregular ventricular morphology among other features. However, these criteria may overlap because destruction of the brain may be associated with a malformation.
Many CNS malformations, including commissural and histogenetic disorders, can be identified in utero, and some points merit emphasis. Corpus callosum agenesis (CCA) is the more frequent malformation, but it may be very difficult to achieve the overall evaluation of CA by MR until after delivery. This limitation is particularly true in cases of partial agenesis involving an interhemispheric cyst that, through its mass effect, can prevent the detection of associated cortical dysplasia. Moreover the prognosis of isolated CCA diagnosed in utero is still debated. MRI is very helpful in cystic malformations of the posterior fossa, in which it is better able than US to detect whether the dural structures, mostly the tentorium, are normally positioned or not. The Dandy-Walker malformation with either closed or open cyst is characterized by an elevated tentorium (well above the inion), the bulging of the parieto-occipital vault, the partial or total
absence of the vermis. The retrocerebellar pouch (expansion of the Blake’s pouch) also shows a
tentorium that is too high with a normal development of the vermis and is part of the Dandy
continuum 19. In contrast a small posterior fossa is seen in Chiari malformation. A normally
positioned tentorium is seen in malformations within a posterior fossa of normal size, such as
ponto-cerebellar hypoplasia, rhombencephalosynapsis, and rhombencephaloschizis. Cerebellar
hypoplasia is difficult to assess because cerebellar development is quite slow with cellular
migration continuing until one year of age. Severe hypoplasia and rhombencephalosynapsis,
which have poor prognosis, are easy to identify.

MRI identification of histogenetic disorders, which are rarely suspected on US, can enable
genetic counseling for future pregnancies. These abnormalities can be summarized as: 1)
disturbance in cell proliferation leading to microlissencephalies; 2) disturbance in cell
differentiation giving focal cortical dysplasia including tuberous sclerosis; 3) disturbance in cell
migration resulting in heterotopia, and lissencephalies (agyria-pachygyria), and 4) disturbance in
organization of the cortex leading to micropolygyria. Identifying abnormalities of cortical
development is not always easy, especially in young fetuses from 18 to 25 weeks, because the
brain is normally agyric at that age. Attention has to be given to the absence of the multilayered
pattern of the cerebral mantle, the absence of the normal signal of the cortex, these findings being
suggestive of cortex/white matter abnormality as pointed out by Fogliarini and al [30]. However
microlissencephalies are usually diagnosed in the third trimester provided the head circumference
is three standard deviations below the mean.

A number of conditions can lead to destruction of the fetal brain, such as hypoxia, congenital
infections (especially toxoplasmosis and cytomegalovirus infections) 45, malformation (vascular
and heart malformations), pregnancies at risk of brain damage, inherited inborn error of
metabolism, especially mitochondrial diseases, and tumors. The chronic responses of the brain, or
the combination of chronic and acute response, are more commonly seen than an acute response
alone, as opposed to what is seen in the neonatal period, because the physiologic conditions are
completely different. Calcifications and malformation of the cortex are most likely seen in cases
of congenital infection but not exclusively because hypoxia-ischemia is known to interfere with
cortical organization, as in cases of twin-to-twin-transfusion syndrome when death of a co-twin
occurred earlier than 20 weeks of gestation. Chronic responses often manifest as mild
ventriculomegaly, with irregular ventricular wall, nodular and irregular germinal matrix. White
matter gliosis and ependymal abrasion is almost always seen at autopsy. Diffusion imaging and proton spectroscopy will help detect such cases.

Ventriculomegaly, which is caused by malformation, destructive lesion, and more rarely by tumor, can be seen in numerous syndromes. An apparent mechanism for ventricular dilatation is not always found in utero, as opposed to the postnatal period. The prognosis for ventricular dilatation in the fetus is poor. Findings indicative of a more favourable outcome include isolated ventriculomegaly, late diagnosis (third trimester), slow evolution, and a ventricle-hemisphere ratio of no more than 50% of normal. Prognosis depends on the cause for the ventricular dilatation, which can be quite challenging to determine prenatally.

Developmental delay in mild isolated ventriculomegaly (whether uni- or bilateral) ranges from 19 to 36%. The underlying mechanism of isolated ventriculomegaly can involve: 1) fetal hypoxia (7% of cases in our experience); 2) early stage of benign external hydrocephalus (16% in our experience), especially when associated to prominent subarachnoid spaces in the parietooccipital areas; and 3) subtle changes of the white matter. Proton spectroscopy and diffusion will probably help depict cases with gliosis and hypoxic-ischemic metabolic pattern.

CONCLUSION

MRI can be a critically important complement to US, especially in pregnancies at risk of brain damage. Technical advances, such as diffusion and proton spectroscopy, will help establish a greater understanding of mechanisms involved in normal and abnormal brain development.

REFERENCES