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MINISYMPOSIUM

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New advances in fetal MR neuroimaging

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Abstract MR is now routinely and widely used in fetal neuroimaging and has proven to be valuable in the detection of many cerebral lesions, either genetically determined or acquired in utero. However, its efficiency has certain limits in the detection of diffuse white-matter abnormalities, the evaluation of fibre development and the demonstration of metabolic disorders. Moreover, conventional fetal MR imaging provides only a morphological approach to the fetal brain. New techniques such as diffusion-weighted imaging, diffusion tensor imaging, proton MR spectroscopy and functional MR imaging are developing. The majority of these are not used routinely. The principles, aims, technical problems and possible applications of these techniques for imaging the fetus are discussed.

Keywords Brain · MRI · Fetus

Introduction

MR imaging is now routinely and widely used in fetal neuroimaging. However, after 15 years of use, conventional fetal MR imaging has recognized limitations, and it is therefore necessary to develop new fetal MR neuroimaging techniques. The aim of this article is to review the limits of conventional MR imaging and to evaluate the advances that may be expected from the following new techniques: diffusion-weighted imaging (DWI), proton MR spectroscopy (H-MRS) and functional MR imaging (fMRI). For each technique, the principles, aims and possible applications are discussed.

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Why are new advances in fetal MR neuroimaging necessary?

Conventional fetal MR imaging allows a morphological evaluation of the fetal brain. Unlike US imaging, MR imaging gives information regarding true cerebral biometry, and normal biometric data of the supratentorial space and posterior fossa have been established [1]. The phenomenon of gyration has also been studied using fetal MR imaging and the chronology of the appearance of the various sulci has been established [2]. The study of the cerebral parenchyma appears much more complex, and the reasons for this are twofold:

1. Ethical
   It is not possible to perform fetal MR in the normal fetus. The normal fetus is regularly studied using US. Therefore normal variants may be easily correlated with gestational age and the equipment used. Conversely, few MR series of normal fetal brains are available and not all normal variants are known. As an example, the T2 hyperintensity of the temporal lobes and the centrum semiovale can be considered normal, but many other variants remain uncertain (Fig. 1).
2. High water content of the fetal brain
   The high water content of the immature nonmyelinated fetal brain accounts for the poor contrast in the cerebral parenchyma and consequently leads to difficulties in detecting diffuse lesions. Because MR gives better contrast resolution than US and better visualization of some territories, for example the temporal lobes, focal signal abnormalities are more easily depicted with MR and this has proved particularly useful in the detection of focal ischaemic lesions. Conversely, the demonstration of diffuse white-matter (WM) abnormalities remains a challenge with MR, and this is of paramount importance in the detection of the early stages of hypoxic–ischaemic damage [3, 4] (Fig. 2). Moreover, MR has a key role in the detection of cerebral ischaemia because the clinical and biological contribution is poor and US has poor sensitivity for the detection of some lesions. One can rely on few indirect

sonographic signs such as polyhydramnios (related to swallowing impairment), decreased fetal movements and ex vacuo ventriculomegaly. The direct signs of ischaemia are not consistent and may be totally overlooked on US imaging.

Because of poor sensitivity of sonography and to a lesser extent of conventional MR imaging, there is undoubtedly a necessity to refine the morphological approach and to add metabolic and functional studies.

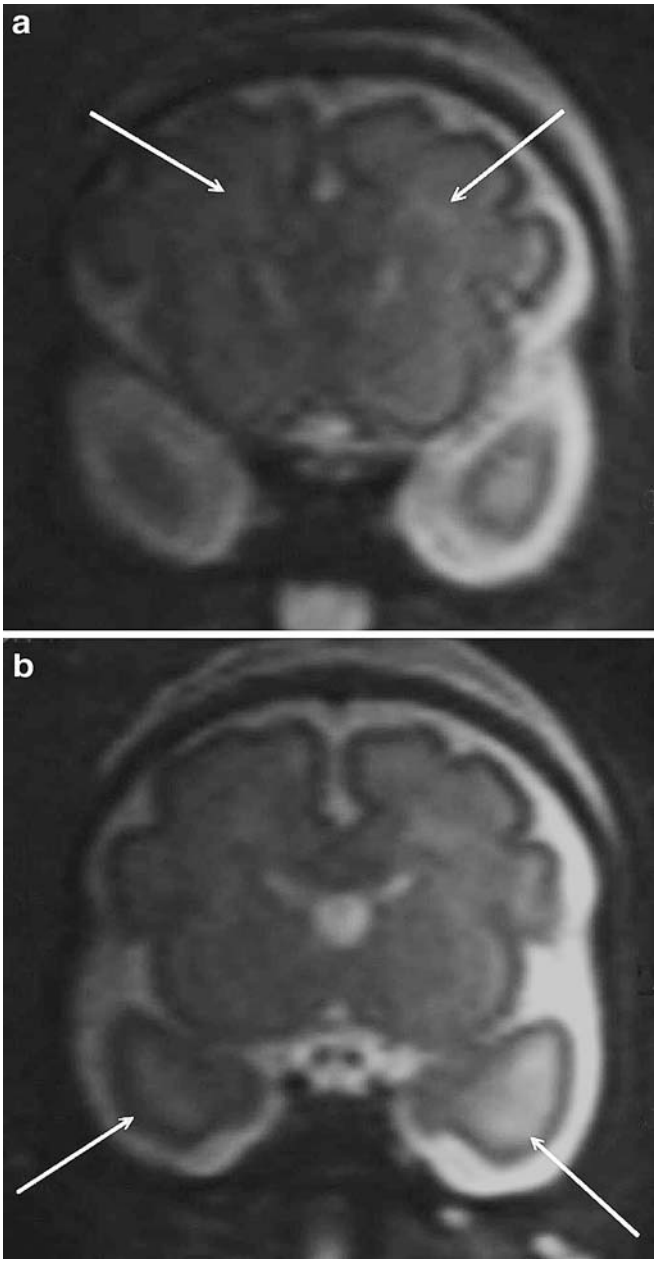

Fig. 1 Normal variants on T2-W images. Coronal slices in a fetus at 30 weeks of gestation. **a** At the level of the frontal horns there is bilateral hyperintensity (*arrows*) in the centrum semiovale. **b** At the level of the temporal horns there is bilateral hyperintensity (*arrows*) in the temporal lobes

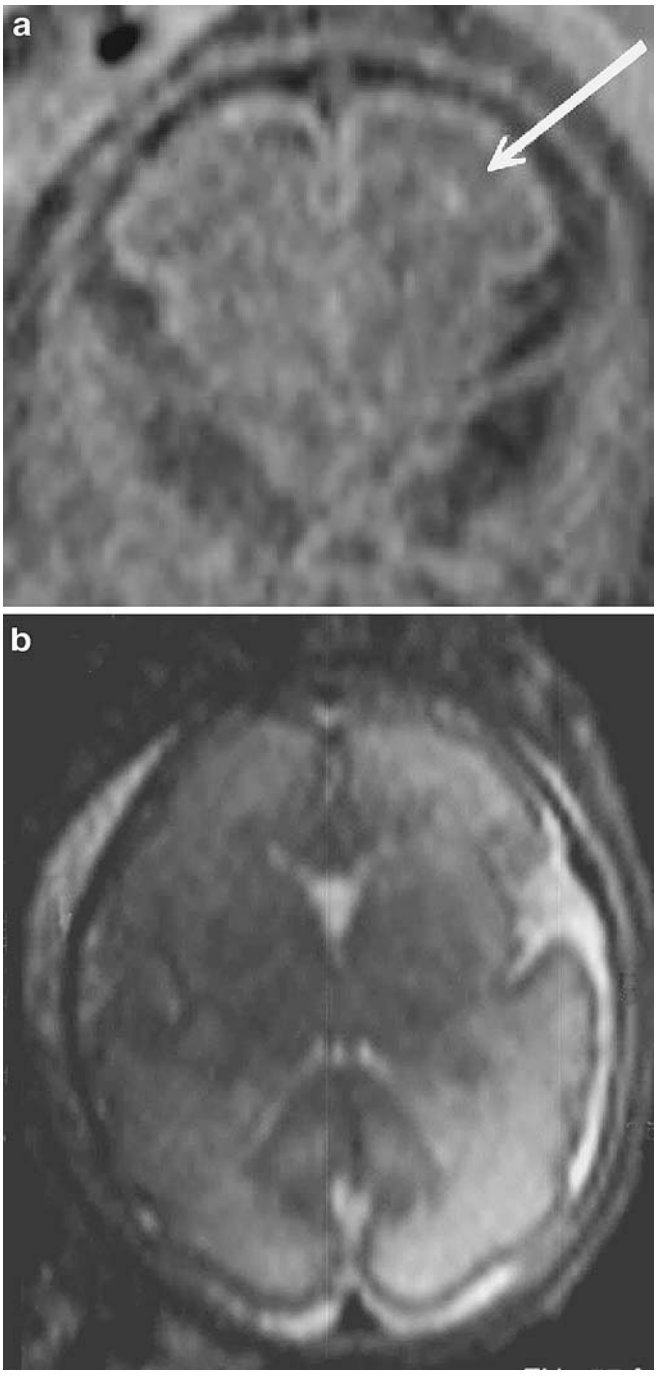

Fig. 2 Ischaemic lesions. **a** Left frontal calcified leukomalacia (*arrow*) appearing as a focal T1 hyperintensity. **b** Diffuse T2 hyperintensity (hypointensity on T1 images) of the WM in a fetus with intrauterine growth retardation and cerebral vasodilatation. With such diffuse lesions the diagnosis of ischaemia is much more difficult to establish

Three new techniques are available and are discussed. DWI is routinely developed in a few centres, whereas H-MRS and fMRI are part of research protocols in a few centres and are not used in routine practice.

DWI and diffusion tensor imaging

Principles

DWI reflects the Brownian motion of water molecules within the brain which can be evaluated by measuring the apparent diffusion coefficient (ADC). It has proved valuable after birth for detecting the early stages of hypoxic–ischaemic damage and various WM disorders. Diffusion tensor imaging (DTI) provides information on the direction of the WM tracts (anisotropy) and depends on tissue structure and the direction of the applied gradient.

Technical problems encountered in the fetus

DWI is performed using echo-planar imaging. It is a very noisy sequence that is very sensitive to motion artefacts. Moreover, spatial resolution is poor, which may lead to a partial volume effect. The acquisition time is short (less than 1 min). As a result of the high water content of the fetal brain, the phenomenon of diffusion is amplified. At the present time, fibre tracking is not routinely used in the fetus.

Aims of fetal DWI and DTI

The aims of this technique are to assess maturation-dependent microstructural changes of cerebral WM (including establishment of normal values of fetal brain ADCs) and to detect diffuse WM abnormalities. DWI can also be useful in detecting old and small haemorrhagic foci [5]. DTI should be a useful technique for evaluating fibre development, for example in the vicinity of gyration abnormalities or in association with corpus callosum agenesis. The anisotropy index increases with brain maturation and different patterns of fibre tracking can be seen with changing gestational age.

In utero brain maturation demonstrated by DWI

DWI changes have been shown in postnatal studies of both premature and term newborns. During brain maturation, there is a progressive decrease in total water content within the brain and an increase in lipid concentration. The so-called ‘premyelinization’ state is characterized by progressive water movement restriction with a decrease in ADCs and restriction of water diffusion directionality with an increase in anisotropy. ADC mapping has been established in newborns [6–10].

In fetuses, mean ADC normal values have been reported in one series of 15 fetuses whose gestational ages ranging from 22 to 35 weeks [11]. The study was performed with a 1.5-T unit (GE Medical Systems, Milwaukee, Wis.). The diffusion gradients were applied in three orthogonal axes with two b factors (0 and 600 s/mm^2) per axis. The mean ADC values were established in frontal WM (1.96±0.1 μm^2/ms), in occipital WM (1.95±0.1 μm^2/ms) and in the basal ganglia (1.56±0.1 μm^2/ms). The authors observed a progressive decrease in ADCs in the basal ganglia throughout pregnancy and a trend towards a decrease in the frontal WM.

In our institution, we have examined 24 fetuses with gestational ages ranging from 31 to 37 weeks on a 1.5-T unit (Intera, Philips, The Netherlands). Diffusion gradient (b=0 and 700 s/mm^2) was applied in six non-collinear directions and mean ADC values were 1.8 μm^2/ms in the centrum semiovale, 1.2 μm^2/ms in the splenium of the corpus callosum and 1.2 μm^2/ms in the pyramidal tract (anterior part of the cerebral peduncle). We observed a decrease in ADCs with gestational age in the pyramidal tract and the corpus callosum (with significantly increased fractional anisotropy) and a trend towards a decrease in the centrum semiovale [12].

Detection of fetal cerebral abnormalities with DWI

The main challenge of DWI in the fetus is the early detection of lesions in risk situations that will lead to cerebral ischaemia prior to the establishment of irreversible damage.

Unlike what is observed in neonates, acute ischaemic lesions are much less common in the fetus than diffuse chronic lesions. The typical pattern of cytotoxic oedema and marked decrease in ADCs in the basal ganglia and the pericentral cortex seen in term neonates secondary to marked and sudden hypoxia is unlikely to be seen in the fetus. In the antenatal period, chronic ischaemic damage related, for example, to fetal infection or placental insufficiency is much more common. Consequently, increased ADCs in the white matter are more likely to be observed.

In a recent study [13], WM damage was analysed in rats within the context of an animal model of gestational hypoxia. Protracted gestational hypoxia in pregnant rats with a perinatal reoxygenation phase was responsible for WM injury. At birth, WM lesions were associated with microglial activation and increased ADCs. Increased activated macrophage counts were observed in the WM. Subsequently, glial scars were associated with relatively decreased ADCs. Defects in myelination were due to immature oligodendrocyte cell death [13].

As yet, there is no published series reporting the contribution of DWI to the detection of cerebral ischaemic lesions. However, it is likely that such a technique will be very helpful, especially when WM T2 hyperintensity is observed in a situation known to lead to impairment of fetal brain perfusion. Objective analysis of WM by measuring ADCs should contribute.

Proton magnetic resonance spectroscopy

Principles

H-MRS is a non-invasive tool for examining cerebral metabolism. It is based on measurement of the chemical

shift, i.e. the local change in resonant frequency due to different chemical environments. Resonances of various metabolites are identified in order to obtain H-MR spectra.

Technical problems encountered in the fetus

H-MRS is more difficult to perform in the fetus than after birth because the coils used are not dedicated to brain imaging [5]. The distance between the fetal brain and the coil is long. Because of long acquisition times (in utero H-MRS can take 30 min to perform [14]), fetal motion is likely to occur and, therefore, the likelihood of failure is high. As movements are reduced in late gestation, most studies have examined fetuses during the third trimester of pregnancy. In order to reduce fetal motion, maternal sedation and a breath-hold approach have been suggested [14, 15].

The size of the volume of interest (VOI) varies according to the author (4.5 cm^3 for Brunel et al. [5] and 20 cm^3 for Kok et al. [16]. A compromise must be found because if the VOI is too small, the signal-to-noise ratio is reduced, and if it is too large, metabolic information will be acquired from all tissues included within the VOI. Notably, contamination of subcutaneous fat in the fetal scalp will occur [16, 17].

Aims of H-MRS

Normal patterns and normal variants are still not fully determined. Metabolic mapping of the fetal brain at different gestational ages has to be established. When these normal patterns are well known, this technique will aim at detecting early metabolic variations in fetuses with suspected brain damage. Perhaps, in the distant future, it will be possible to diagnose inborn errors of metabolism with H-MRS.

In utero brain maturation demonstrated by H-MRS

This technique is not performed routinely and is currently part of research protocols in very few centres. It is important to remember that:

- *N*-acetyl-aspartate (NAA) is confined to the neurons and axons.
- Creatine (Cr) is involved in cellular energy metabolism.
- Choline (Cho) is a constituent of membranes and plays a role in myelination.
- Myoinositol (mI) is a glial marker.
- Lactates are the end product of anaerobic glycolysis.

H-MRS can help us to observe brain maturation which reflects fetal brain developmental changes. The following data are based on a few recent articles [5, 14, 16–18]. Most authors have studied H-MRS in fetuses after 30 weeks. Brunel et al. [5] have reported results from 22 weeks. At that stage, Cr is clearly visible, whereas NAA is barely detectable. The spectrum is mainly characterized by two prominent peaks assigned to mI and Cho.

Throughout pregnancy, a progressive increase in the NAA peak is observed, which is attributed to maturation of the brain with development of dendrites and synapses. The peak of Cho decreases as myelination progresses. No significant changes are observed for the Cr and mI peaks. Lactates are not detectable.

Detection of fetal cerebral abnormalities with H-MRS

This technique is still very new and little is known about its potential contribution in the evaluation of the pathological fetal brain. A decrease in NAA and an increase in lactates should be predictors of adverse neurodevelopmental outcome. Lactates have already been detected in utero in the basal ganglia of two of six fetuses presenting with hydrocephalus [17]. However, many other observations are necessary to validate fetal H-MRS.

fMRI

Principles

fMRI studies brain activity in response to various stimuli and is based on the BOLD (blood oxygen level dependent) effect. Local neuronal activity increases in response to a stimulus, inducing an increase in local blood flow and consequently an increase in venous blood oxygenation and in blood volume, which is known as the haemodynamic response. This leads to an increase in local MR signal known as BOLD contrast. fMRI is performed using echo-planar imaging, which is very sensitive to differences in magnetic susceptibility. The difference between oxy- and deoxyhaemoglobin generates the fMRI signal [19].

Technical problems encountered in the fetus

fMRI is currently used as part of research protocols in only one centre in the world—Nottingham. In this centre fMRI studies have been carried out on a low-field unit (0.5 T). Because the field is low, the advantages include reduced susceptibility artefacts, acoustic noise and tissue heating. Conversely, the signal-to-noise ratio and the BOLD sensitivity are decreased, which are major disadvantages. There are further problems related to motion artefacts because of a long acquisition time of about 20 min. In order to reduce motion, imaging is performed in fetuses in the cephalad position and late in pregnancy (after 36 weeks) when the fetal head is engaged in the maternal pelvis.

Another problem concerns the acoustic noise during the acquisition of the images, which is loud for echo-planar imaging but attenuated by the maternal abdomen and the fluid filling the ear [19].

Aims of fMRI

The main purpose is to add a functional study to the morphological approach to the fetal brain to provide information regarding functional cerebral development. When normal data are known, it should become possible to observe changes in functional brain development in various pathologies. For example, when a fetus presents with septal agenesis, it is currently impossible to ascertain if there is associated septo-optic dysplasia because the spatial resolution is too poor to satisfactorily evaluate the optic tract. We hope that in the future fMRI will enable us to evaluate the visual function of these fetuses.

Two types of stimuli have been used: vibroacoustic and visual stimulus.

Vibroacoustic stimulus With headphones strapped to the maternal abdomen a sound level of 95–100 dB was generated. Activation was observed in the temporal lobe of 7 of 15 fetuses [20].

Visual stimulus The visual stimulus was provided by a red LED cluster on the maternal abdomen. Ultrasonography was performed before fMRI to ensure that the fetal eyes were directed towards the maternal abdomen. The light source was positioned in order to overlay the fetal eyes. In three of eight fetuses, activation was not found. In four of the five fetuses with activation, the area was found within the frontal region with no significant activation detected within the visual areas [21].

The haemodynamic response is different in fetuses than in adults. This may reflect differences in the oxygen affinity of fetal and adult haemoglobin, immaturity of vascular control mechanisms, differences in activation in the immature brain (immaturity of the synaptic connections precluding neuronal activity in the usual cortical area of interest) and low sensitivity of the fetal fMRI technique [19].

In conclusion, conventional fetal MRI remains mandatory for studying fetal brain morphology. DWI is routinely developed in some centres but its contribution is not yet fully evaluated. However, it is very possible that this technique will be of interest in the detection of early ischaemic damage. H-MRS and fMRI are still part of research protocols, but will probably develop in the near future.

We certainly have to be concerned about these new techniques and to wonder whether they are safe or not. To date, we do not know if high gradients, intense light or high-level sounds are safe for the fetus, and follow-up of these patients after birth is essential. In order to determine normal values of the fetal brain with these new techniques, large cohorts of fetuses need to be studied, and this in turn raises ethical and practical problems as these techniques dramatically lengthen the examination time.

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