

## Diffusion MRI in the Fetus and Newborn

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### Introduction

After becoming fundamental tools in adult clinical neuroradiology, diffusion-weighted imaging (DWI) and diffusion tensor imaging (DTI) have been successfully applied in research and clinical imaging of neonatal brain (1, 2). More recently DWI and DTI research and clinical applications in *in-vivo* fetal brain imaging have been reported (3 - 5). DWI and DTI applications in the fetus and newborn require some methodological and technical adjustments with respect to the usual practice in adult patients. In particular, a more rapid acquisition strategy in order to reduce motion artefacts is needed. Moreover, the specific tissular structure of the developing brain requires optimisation of the diffusion sensitising parameters in the sequence.

### Methodological aspects

For the *in-vivo* fetal brain DWI at 1.5 T we use a circular surface coil or an abdominal phase-array coil. We use the former in thin mothers and for fetuses of early gestational age (GA) (usually before the 24<sup>th</sup> week of gestation), since the sensitivity field of this small coil is sufficiently large to cover the volume of such small brains; possible signal inhomogeneity is compensated for by the higher signal-to-noise ratio we obtain and by the option of increasing the spatial resolution. In more advanced pregnancies the abdominal phase-array coil improves signal homogeneity, albeit at the price of lower spatial resolution; the latter can be compensated for by the larger size of the brain of older fetuses. The breath-hold DWI sequence is a spin-echo echo-planar (SE-EPI) one with 3 directions diffusion-sensitised gradients. Slice thickness is 4 to 5 mm, FOV is between 260 and 320 mm, matrix = 128 x 128, TR is between 1200 and 3000 ms, TE is as short as possible (usually between 58 and 70 ms, depending on scanner gradient strength). We can obtain 5 to 10 axial sections in an acquisition time between 7 and 14 sec, which is compatible with the ability of the average pregnant woman to hold her breath. Fetuses are not sedated. Volume shimming is localized at fetal head level. The b-factor of diffusion-sensitised images is between 600 and 700 s/mm<sup>2</sup>. The use of a breath –hold compatible sequence is needed to minimize image distortion due to motion artefact. Nevertheless, motion can still affect images, especially if the head of the fetus is located close to the diaphragm or aorta; for this reason the DWI sequence is often repeated three or four times in order to increase the chance of acquiring better images. A special issue is the one related to the b-factor value to be used, which is lower than the one used in adult DWI. Lower b-factor values allow diffusion-weighted images to be obtained with better signal-to-noise ratio. Moreover, the water diffusivity process within the brain seems to have two components: a fast one and a slow one. The fast component seems to prevail in the fetal as well as in the premature newborn brain, at least as compared to the adult brain (6). The lower b-factor value we use may therefore be preferred in investigating normal fetal brains; however, in case of pathological ADC reduction, as in acute ischemia, when the slow component may prevail, the use of lower b-values could lead to an underestimation of the degree of ADC reduction (this issue has not been explored yet).

To study water diffusion changes in the newborn brain at 1.5 T we use a quadrature coil of 18 cm diameter, similar to the one used for knee imaging. This coil improves signal-to-noise ratio to be obtained, especially as compared to the larger standard phase array 8-channel head coil. Moreover, since we do not usually apply parallel imaging (i.e. SENSE) in the unsedated newborn, because of motion artefact risk, we do not need to use the latter coil. DTI on newborns is performed with the same coil, adopting a SE-EPI sequence with six directions diffusion sensitized gradient (TR/TE = 5000/58 msec, voxel size = 1.5 x 1.5 x 3 mm, 23 contiguous slices, 1 nex, b-factor value = 700 s/mm<sup>2</sup>). We choose this fast sequence (only 1 nex and about 40 sec. acquisition time) with coarse spatial resolution and with a lower number of diffusion gradient directions, not to be constrained by the use of complex motion correction post-processing in clinical routine practice.

We have recently performed also DTI of the fetal brain *in-vivo* by mean of a SE-EPI sequence with six-directions diffusion-sensitized gradients. The sequence takes advantage of phase-array abdominal coil and of parallel imaging technique (i.e. SENSE) to keep image acquisition time below 20 sec, so as to be compatible with the maximum duration of breath-holding by the mother (TR/TE = 2200/58 msec, voxel size = 2.72 x 2.72 x 5 mm, 9 contiguous slices, 1 nex, b-factor value = 700 s/mm<sup>2</sup>). However, with respect to the three-axes diffusion-sensitized sequence the possibility of collecting data free from motion artifacts is remarkably lower (6).

### ADC and DTI in the normal brains of fetuses and neonates

The ADC determination of normal developing brain is essential for the use of DWI in clinical settings. In normal fetal brains (GA range between 21 and 36 weeks) the average ADC values have been reported (3) to be between 1.8 and 1.9  $\mu\text{m}^2/\text{ms}$  in frontal and occipital unmyelinated white matter (UMWM) and between 1.4 and 1.5  $\mu\text{m}^2/\text{ms}$  in the gray matter of basal ganglia (BG). ADC values in fetal brains tend to decrease with increasing GA. This could be related to a decrease in water content and to an increase in cell membrane density associated with brain maturation. Other authors (7) have reported that in UMWM (i.e frontal areas) ADC has a biphasic course: it increases after the 20<sup>th</sup> week up to the

27-28<sup>th</sup> week and then decreases progressively. This discrepancy could be related to the fact that ROI measurement in WM (especially in frontal regions) may include the so-called intermediate zone of late migrating cells, where cell bodies are quite dense before the 25<sup>th</sup> week, as they tend to spread towards the cortical rim later on. Analyzing data based on three-axes diffusion-sensitizing sequence and with DTI acquisition, we found that fractional anisotropy (FA) is noticeable even in unmyelinated areas (i.e. corpus callosum) starting from the 20<sup>th</sup> – 21<sup>st</sup> week of GA. This is probably related to the so-called premyelination anisotropy: axons in WM become thicker and their membrane less permeable to water molecules along with brain maturation, even in the absence of obvious myelination. In normal term newborns (2, 8-10) the average ADC value has proved to be between 1.6 and 1.8  $\mu\text{m}^2/\text{ms}$  in frontal and occipital UMWM, between 1.0 and 1.1  $\mu\text{m}^2/\text{ms}$  in the posterior limb of internal capsule (PLIC) myelinated white matter (MWM), and between 1.2 and 1.3 in BG gray matter. At term FA is clearly present not only in MWM areas as pontine tegmentum longitudinal pathways and PLIC, but also in UMWM areas as corpus callosum, corticospinal tracts, anterior limb of internal capsule, external capsule, and optic radiation, confirming the phenomenon of premyelination anisotropy. Postnatal studies in premature babies have shown a general decrease of ADC with GA in BG, MWM, and UMWM. On the other hand, FA tends to increase with GA within corticospinal tract or PLIC. However, the phenomenon accelerates significantly only in the very last weeks of gestation. Recent DTI analysis of premature cortex (11) shows that the cortical rim is inherently anisotropic before the 30<sup>th</sup> week of gestation, because of the prevalence of radial distribution of cells within developing cortex. FA decreases towards term, as the tridimensional structure of cortical layers becomes more complex. In some areas, with more advanced maturation at term (i.e. perirolandic cortex), the FA reaches lower values earlier than in other areas (i.e. cortex of frontal pole) (12)

#### *Clinical DWI applications on fetal brain*

We acquire diffusion-weighted images, as part of our standard fetal MRI protocol in cases where clastic lesions, brain masses or complex brain malformations are suspected on the basis of ultrasound or clinical findings. Acute focal ischemic lesions with remarkable decrease in ADC have been demonstrated in cases where conventional images were still uninformative (4). In other cases with focal ischemic lesions already visible on T2-weighted images ADC measurement helped to establish the sub acute nature of the lesion. In cases with intracranial masses DWI helped in establishing the fluid nature (arachnoid cyst) of cystic masses, differentiating them from epidermoid cysts (solid) or intraventricular masses (i.e. choroid plexus cysts versus intraventricular neoplasms (solid)). Regarding DWI and fetal brain malformations, we recently reported (13) a particular case of macroencephaly in which ADC was clearly decreased within the basal ganglia-germinal matrix region, suggesting the presence of hypercellularity with consequent hindering of water motion. That is in agreement with what was reported in some hypercellular neoplasms (14). In this macroencephaly case a probable increase in cellular proliferation or a decrease in apoptosis occurred as an abnormal phenomenon before the 20<sup>th</sup> week of GA, resulting in hypercellularity. ADC determination can contribute to the assessment of white matter alterations, which occur during intrauterine infections (i.e. toxoplasmosis, cytomegalovirus, etc.), where ADC often increases as a result of tissular edema and rarefaction. A white matter ADC increase can be observed also in severe congenital anomalies as Arnold-Chiari type II malformation: in this case a chronic insult to white matter might be secondary to mechanical compression of the brain or to venous congestion associated with severe intracranial volume reduction and dysmorphic posterior fossa. The full extent of DWI applications on fetal brain pathology remains to be explored; the near future hardware and software improvements are likely to facilitate DWI in this field.

#### *Research applications of DTI in the study of brain anomalies in very premature babies*

Work has recently been performed using DTI to assess how prematurity itself affects brain development (8, 9). Of particular interest are those cases in which only minimal WM lesions are visible at conventional MR imaging. The ADC value in WM regions of premature babies studied at term has been found to be moderately higher than in full-term controls. FA has been reported to be lower in WM of preterm infants. These DTI studies confirm that some impairment of brain maturation can affect preterm babies, supporting the clinical observation that ex-preterm children are at higher risk of developing neurological impairment.

#### *DWI and white matter injury in preterm babies.*

Periventricular leukomalacia (PVL), which represents one of the main neurological insults in preterm neonates, has been extensively investigated by conventional MR imaging, which usually shows areas of obvious WM necrosis or cavitations. Recently, a clear and early ADC decrease (15) was demonstrated in WM areas of premature babies who developed classical PVL signs on conventional MRI later on. This early ADC decrease, within the so-called diffuse component of PVL, supports the idea that some ischemic-like mechanism may play an important role. Moreover, the possibility of detecting such an early and diffuse PVL component is of great interest, as it could be the target of future therapeutic and neuroprotective strategies.

*Applications of DWI in hypoxic-ischemic encephalopathy in full term newborns.*

Hypoxic-ischemic encephalopathy (HIE), which is the main cause of morbidity in full-term neonates, has been extensively studied with DWI in several protocols (16-18). In the acute phase ADC decrease may be observed in basal ganglia, hippocampus, watershed cortical areas, diffuse in white matter or localized in PLIC white matter, or in all these regions in different combinations. While in a first, very early phase, water diffusion restriction seems related to the development of neuronal cytotoxic edema, in a delayed phase after brain reperfusion, ADC decrease seems mostly related to the massive swelling of astrocytes. The judgment about the role and the accuracy of diffusion imaging in HIE is complicated by the large amount of variables that influence the data analysis in the papers on this issue. Pathophysiologic variables, such as the degree and duration of the hypoxic-ischemic insult, the co-existence of additional insults (i.e. hypoglycemia) or technical factors, such as not only the timing of scanning, but also the quality of the T1-weighted images to be compared with DWI, influence the outcome of diagnostic accuracy studies. Nevertheless, some conclusions about DWI and HIE are sufficiently supported by the present literature: 1) DWI is more sensitive to early damage (ADC decrease) than conventional MRI in the first two days from insult onset. 2) In the first two days DWI often underestimates the extent of the damage. 3) There is no certain cut-off value below which ADC decrease in acute phase heralds irreversible damage; however, diffuse ADC reduction throughout the brain below  $0.7 \mu\text{m}^2/\text{ms}$  is very often associated with lethal outcome. 4) An ADC reduction below  $0.6 \mu\text{m}^2/\text{ms}$  in PLIC white matter in the first five days is associated with very poor neurologic prognosis. 5) ADC normalization or pseudonormalization occurs in about seven days. 6) The presence of abnormal lactate peak at proton spectroscopy is more sensitive than DWI when the baby is examined in the acute phase.

*DWI in acute arterial infarction in the newborn and wallerian degeneration.*

Focal ischemia in an arterial territory occurring in the first days of life is a rare event, which can be diagnosed more frequently than in the past, thanks to the advent of MRI. The early diagnosis can be difficult, because the clinical signs in the acute phase are usually confined to the onset of seizures and because transfontanellar ultrasound is often negative. DWI has proved to be very sensitive in this situation (19). Moreover, it shows a different ADC time course from the one observed in adult patients, since in neonates ADC-pseudonormalization occurs earlier (by about one week) than in adults. This phenomenon may be related to the higher water content, the scanty myelination, and the different cerebral blood flow value of developing brain. The initial signs of wallerian degeneration in the corticospinal tract of newborns with infarction can be detected very early (as early as two days after the event) by DWI as a focal area of decreased ADC (20). The depiction of wallerian degeneration can be of value, because it heralds a poor neurological outcome.

*DWI in severe neonatal hypoglycemia*

Neonates undergoing severe hypoglycemia (due to endocrinologic or metabolic causes), typically develop diffuse lesions in the parieto-occipital areas (21). In the early stage a clear ADC decrease can be observed in these areas, especially at cortical rim level (22). The water diffusion restriction seems to be related to cortical neuron cytotoxic edema with prominent dendritic swelling; this acute process is often irreversible and leads to neuronal necrosis.

*ADC changes during osmotic brain perturbation.*

We recently reported (23) on diffuse brain ADC decrease during correction of severe hypernatremic dehydration in a neonate. In this case i.v. water was excessive in relation to the compensatory intracellular idiogenic osmoles accumulation; the water in excess shifted from the extra cellular to the intracellular environment leading to cellular swelling (osmotic edema). Osmotic edema, which was fully reversible in our case, can resemble cytotoxic edema, as the change in intracellular-to-extra cellular compartment volume ratio is similar. The increase in intracellular volume at the expense of the extra cellular one seems to hinder water molecule diffusivity.

*DWI and neonatal onset of metabolic encephalopathies.*

Brain changes in neonates affected by metabolic diseases are often not easily detected, because of the limited sensitivity of T2-weighted images in highlighting lesions in UMWM long T2 structures. Even when T2 signal abnormalities are found, conventional imaging still provides poor specificity. According to our experience and to data in the literature, DWI and especially ADC calculation may increase MRI sensitivity and specificity in this field. In particular, in the case of reduced ADC, the differential diagnosis is restricted, since so far a very limited number of acute metabolic encephalopathies have been associated with decreased water diffusion (24 - 26). On the other hand, ADC increase may be noticed in the acute and the chronic stage of several other metabolic diseases affecting the brain, so the latter observation is quite unspecific and of little interest. The brain response to toxic-metabolic insult, in regard to water diffusion properties, depends on the microscopic structure of its tissue. In myelinated white matter (deep cerebellum, brainstem, and PLIC) cytotoxic edema takes the form of the so-called intramyelinic edema: water molecules accumulate within the myelin layer, splitting the myelinic lamellae at the intraperiod line level, forming vacuoles, and producing an ADC reduction. These features have been demonstrated so far in nonketotic hyperglycinemia encephalopathy and in acute maple syrup urine disease (MSUD) in the neonate. In MSUD intramyelinic edema in MWM (decreased ADC) has been shown to coexist with vasogenic edema which develops in UMWM (increased ADC), confirming that areas with different histology respond differently to the same toxic insult. In other neonatal metabolic encephalopathies as citruinemia (27), cytotoxic edema affects mostly the cortical and BG

grey matter, where ADC reduction seems mostly related to severe astrocytic swelling: increased intracellular osmolarity because of glutamine accumulation would induce cell swelling.

#### *DWI in neonatal meningoencephalitis*

There have been some reports on DWI findings in children affected by acute infectious diseases of the central nervous system (28), which showed that DWI is able to detect small acute cortical and deep white matter infarcts due to septic vasculitis. Brain infarctions are the most common cause of poor neurological prognosis in infants affected by bacterial meningoencephalitis.

#### *DTI and Fiber Tracking applications in abnormal neonates*

Recently, fiber tracking algorithms have been applied to neonates carrying brain anomalies. Some congenital anomalies with brain dysmorphisms are not easy to be characterized by simple conventional images. We found that in some cases the 3D fiber tracking depiction of the main WM pathways contributed to the understanding of such structural anomalies. In particular, cases with complex midline structures malformations (corpus callosum partial agenesis, fornix anomalies, etc..) or with cortical malformations took advantage of this approach (29, 30). Although current fiber tracking techniques are far from being an accurate quantitative method for studies across subjects, nevertheless there have been very recent attempts to quantify the amount of “spaghetti” fibers in some WM pathways of the newborn brain (31).

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