Diffusion Weighted Imaging in Pediatric Body: Update

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Outline

- Principles of diffusion weighted imaging (DWI)
- Technique of diffusion weighted imaging (DWI) in pediatric body MRI
- Normal signal intensities of various body tissues on DWI in children.
- Emerging applications of diffusion in pediatric body imaging.
Principles

- Diffusion = random motion of water molecules

- The variation in mobility of water molecules between different tissues results in different signal intensity on diffusion imaging

- Isotropic diffusion = chance that molecule will move in any direction is equal  
  Routine DWI

- Anisotropic diffusion = molecules move in a preferential direction e.g. along fiber tracts  
  DTI

What does diffusion tell us?

- Increased diffusion
- Decreased diffusion

- The signal intensity on DWI indirectly informs us about the microenvironment within the tissue.
Technique: diffusion weighting and b-value

- **b-value** = degree of diffusion weighting
- **b-value** (sec/mm²) depends on and increases with the amplitude, duration of application and separation of diffusion gradients (DG).
Technique: diffusion weighting and b-value

- As b-value increases sensitivity of the sequence to the diffusion increases and signal from the water molecules reduces.

$B = 0$

Technique: diffusion weighting and b-value

- As b-value increases sensitivity of the sequence to the diffusion increases and signal from the water molecules reduces.

$B = 100$
Technique: diffusion weighting and b-value

- As b-value increases sensitivity of the sequence to the diffusion increases and signal from the water molecules reduces.

Technique: diffusion weighting and b-value

- At high b-value, tissues with reduced water molecule mobility, long T2 relaxation time or both will have high signal.
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**Technique: choice of b-values**

- Minimum 2 b-values required for ADC calculation
- **Depends on** –
  - The organ of the interest
  - T2-value of the organ e.g. T2 of liver is approx 46 ms as compared to 90 ms for gray matter.
  - The purpose - lesion detection versus characterization
  - To certain extent - field strength
- **Choose** -
  - Low b-values (50-100) - for lesion detection
  - High b-values (600-800) - for lesion characterization
  - Very high b-values (1000-1500) - for DWIBS

**Typical b-values in children (sec/mm²)**
- Liver: 0, 100, 600
- Renal: 0, 100, 800
- Bowel: 0, 400, 800
- MSK: 0, 400, 800

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**Technique: sequences**

1. **Single-shot fast spin-echo echo-planar sequence**
   - Most frequently used sequence
   - Can be acquired with
     - Breath-hold
     - Respiratory triggering
     - Free breathing

2. **DWIBS (Diffusion weighted imaging with background body signal suppression)**
   - Free breathing
   - Heavy diffusion weighting (b-values 1000-1500 sec/mm²)
   - Fat suppression by inversion pulse or CHESS
   - Only structures with restricted diffusion seen on final images
   - Used for Whole-body DWI
Assessment

**DWI**: Qualitative assessment

- Typical diffusion images available for review: b-value 0, highest b-value (diffusion-weighted image) and ADC map

- **DWI bright, ADC dark** = diffusion restriction (eg. Spleen, spinal cord)
- **DWI dark, ADC bright** = increased diffusion (eg. CSF in spinal canal)
- **DWI bright, ADC bright** = T2 shine through (eg. Gallbladder)
- **DWI dark, ADC dark** = proton poor tissue/susceptibility (eg. Bone cortex)
**DWI: Quantitative assessment- ADC**

- ADC maps are derived from multiple b-value images.

**ADC measurements:**
Approximate ADC in the region of interest (ROI) in:
- **Liver (L):** $1.41 \times 10^{-3}$ mm$^2$/sec
- **Kidney (K):** $2.2 \times 10^{-3}$ mm$^2$/sec
- **Spleen (S):** $0.97 \times 10^{-3}$ mm$^2$/sec

**DWI: Quantitative assessment- IVIM**

- IntraVoxel Incoherent Motion
- Mono-exponential vs Bi-exponential
**DWI: Quantitative assessment- IVIM**

- Fast vs slow diffusion

![Graph showing diffusion properties](image)

- $D^*$ = pseudodiffusion - capillary perfusion
- $D$ = pure diffusion - tissue diffusion
- $f$ = perfusion fraction

**DWI: Quantitative assessment- DKI SEM**

- Diffusion kurtosis- DKI
  - Non-Gaussian diffusion behavior
  - Ultra-high b-values >1500-2000
  - $D_{\text{app}}$ and $K_{\text{app}}$
  - Intracellular compartment

- Stretched-exponential model
  - Subvoxel heterogeneity
  - $\alpha$ and DDC
  - Ultra-high b-values upto 5000-6000

*Image from: Rosenkrantz AB, et al. JMRI 2015; 42:1190-1202*

*Image from: Bennett KM, et al. MRM 2003; 50:727-734*
What determines signal intensity on DWI?

1. Mobility of water molecules = ADC
2. T2 relaxation time.

### Normal T2 relaxation time and ADC at 1.5 T

<table>
<thead>
<tr>
<th>Abdominal structures</th>
<th>T2 relaxation time (ms)</th>
<th>ADC ($\times 10^{-3}$ mm$^2$/sec) $^{10}$ (Adults)</th>
<th>ADC ($\times 10^{-3}$ mm$^2$/sec) $^*$ (Children)</th>
<th>ADC ($\times 10^{-3}$ mm$^2$/sec) $^@$ (Children)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spleen</td>
<td>79</td>
<td>1.26</td>
<td>0.93</td>
<td>0.84</td>
</tr>
<tr>
<td>Liver</td>
<td>46</td>
<td>1.55-1.63</td>
<td>1.43</td>
<td>1.1</td>
</tr>
<tr>
<td>Pancreas</td>
<td>46</td>
<td>1.81</td>
<td>1.83</td>
<td>--</td>
</tr>
<tr>
<td>Kidney</td>
<td>87</td>
<td>2.67</td>
<td>1.9</td>
<td>1.85</td>
</tr>
<tr>
<td>Gallbladder</td>
<td>--</td>
<td>3.50</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Back muscles</td>
<td>27</td>
<td>2.13</td>
<td>--</td>
<td>1.22</td>
</tr>
<tr>
<td>Endometrium</td>
<td>101</td>
<td>1.42-1.53 $^{13,14}$</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>


What is normal?: Spleen and spinal cord

- Any lymphoid tissue including normal lymph nodes, spleen and thymus are normally diffusion restricted.
- The spinal cord is normally restricted and may be used as a reference to judge diffusion restriction in other structures.
- Ovary, testis, adrenal glands, neonatal kidneys and red marrow are normally restricted.

What is normal?


<table>
<thead>
<tr>
<th>Structures</th>
<th>Diffusion-weighted (high b value) image</th>
<th>Apparent diffusion coefficient (ADC) map</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymph node, spleen, thymus and spinal cord</td>
<td>Hyperintense</td>
<td>Hypointense</td>
</tr>
<tr>
<td>Liver and pancreas</td>
<td>Intermediate to dark</td>
<td>Intermediate to dark</td>
</tr>
<tr>
<td>Gallbladder and kidney</td>
<td>Hypointense (kidney to lesser extent than gallbladder)</td>
<td>Hypointense</td>
</tr>
<tr>
<td>Ovarian stroma, testicular parenchyma</td>
<td>Hypointense</td>
<td>Hypointense</td>
</tr>
<tr>
<td>Endometrium, central part of corpora cavernosa</td>
<td>Hypointense</td>
<td>Hypointense</td>
</tr>
<tr>
<td>Myometrium, skeletal muscles</td>
<td>Intermediate</td>
<td>Slightly hypointense</td>
</tr>
<tr>
<td>Red marrow</td>
<td>Hyperintense</td>
<td>Hyperintense</td>
</tr>
<tr>
<td>Fatty marrow, epiphysis, bony cortices</td>
<td>Hyperintense</td>
<td>Hyperintense</td>
</tr>
<tr>
<td>Physical and epiphyseal cartilage</td>
<td>Hyperintense</td>
<td>Hyperintense</td>
</tr>
</tbody>
</table>

* Signal intensity relative to skeletal muscles

Clinical applications
Liver Imaging: Lesion detection

- DWI can be used in three ways in liver imaging:
  1. Lesion detection,
  2. Lesion characterization and
  3. Hepatic fibrosis and cirrhosis evaluation.

- **Lesion detection**: Low b-value images (50-100) make vessels dark making easier to detect T2 hyperintense hepatic lesions\(^{22-25}\).

Liver Imaging: Lesion characterization

- In adult studies\(^1,24-27\),
  - malignant hepatic lesions like HCC and mets show low ADC;
  - benign lesions like hemangioma and cysts show high ADC;
  - cellular benign lesions like adenoma and FNH show intermediate ADC.

Path: Hepatoblastoma (*Epithelial-fetal+embryonal*)
Liver Imaging: Lesion characterization

- 89 children: 38 boys; 51 girls with a mean age of 10 years (3 months-18 years)
- Total 112 focal hepatic: 92 benign and 20 malignant
- Final diagnosis: Pathology in 43 lesions; clinical and imaging features and follow up (mean period 21 months) in 69 lesions

Caro-Dominguez P, Gupta A, Chavhan G. Pediatric Radiology In press

Liver Imaging: Lesion characterization

Qualitative DWI assessment

- All malignant lesions showed qualitative diffusion restriction
- Except abscesses none of the benign lesions showed diffusion restriction
- Excluding abscesses, there was significant association between diffusion restriction with malignancy and non-restriction with benignancy (Fisher’s exact test \( p<0.0001 \)).

Caro-Dominguez P, Gupta A, Chavhan G. Pediatric Radiology In press
Liver Imaging: Lesion characterization

Quantitative DWI assessment

- Mean normalized ADC values of malignant lesions [1.23, SD 0.24 (x 10^{-3} mm^2/sec)] was lower than benign lesions excluding abscesses [1.62, SD 0.67 (x 10^{-3} mm^2/sec)].
- This difference was significant using student’s t-test (p<0.015)

Caro-Dominguez P, Gupta A, Chavhan G. Pediatric Radiology In press

Liver Imaging: Lesion characterization

Quantitative DWI assessment

- An ADC value cut-off of $\geq 1.2 \times 10^{-3}$ mm^2/sec yielded a sensitivity of 78% and a specificity of 54% for differentiation of benign from malignant lesion.
Liver Imaging: Lesion characterization

Quantitative DWI assessment

- Significant overlap of normalized ADC between benign and malignant lesions with wide range for each diagnosis

- Restricted liver lesion \[\rightarrow\] Biopsy
- Quantitative (ADC measurements) not yet robust in differentiation.
- The differentiation of malignant from benign lesions is hampered by less reproducibility, variability of ADC measurements up to 30\%; and significant overlap of ADC of benign and malignant lesions\(^4\).

*Caro-Domínguez P, Gupta A, Chavhan G.*
*Pediatric Radiology In press*
Liver Imaging: Lesion characterization

Focal Nodular Hyperplasia

Hemangioma
Spleen as a reference
Liver lesion looking like spleen on all sequences is bad!

Liver Imaging: Fibrosis and cirrhosis

- ADC is reduced in hepatic fibrosis.
- Thought to be related to accumulation of proton-poor connective tissue and reduced capillary perfusion.
- Can be used for detection and quantification of fibrosis and cirrhosis.
- Few pediatric studies showing utility of ADC measurement to predict liver fibrosis, following up severity of cirrhosis* and in Fontan.

Cirrhosis

@ Wolff D, et al. Int J Cardiol 2016 Jan; 202:595-600
DWI can be used in four ways in body tumor imaging:

1. Tumor detection and characterization,
2. Biopsy guidance
3. Monitoring treatment response and
4. Whole-body DWI.

Restricted tumors are usually brightest among all structures making them easier to detect on DWI.

Recurrent renal sarcoma
Body Tumors: Detection and characterization

- Malignant peritoneal thickening and tiny nodular deposits easily detected by DWI.

**Peritoneal deposit from ovarian yolk sac tumor recurrence**

- Adult studies indicate that malignant body tumors tend to be diffusion restricted.
- A few pediatric studies reflect the adult findings\(^{24,58}\).

**Wilms tumor with hepatic mets**
In pediatric studies, neuroblastoma is found to be restricted and has less ADC than ganglioneuroma that may help to differentiate them\textsuperscript{32,33}.

**Body Tumors: Detection and characterization**

- Sarcomas are restricted.

**Body Tumors: Detection and characterization**

- In pediatric studies, neuroblastoma is found to be restricted and has less ADC than ganglioneuroma that may help to differentiate them\textsuperscript{32,33}.
Does restriction in pediatric body tumor means malignant tumor?

- Mostly Yes!
  (we still have to learn a lot)

- Benign neurogenic tumors like schwannoma.
- Benign germ cell tumors especially ovarian

Mature germ cell tumor of ovary
Body Tumors: Biopsy guidance

- Can be used in combination with other sequences for biopsy guidance

Body Tumors: Biopsy guidance

- 2 months later…

*Undifferentiated Sarcoma*
Body Tumors: Therapy response

- ADC increases with therapy.
- In a small pediatric study, hepatoblastoma and Wilms tumor showed increase in ADC with chemotherapy but 2 RMS did not show increase in the ADC despite positive response to chemotherapy on histopathology*.
- Recently, whole tumor ADC predicted response in Wilms tumor®
- Hampered by less reproducibility, variability of ADC measurements and lack of standardization of technique.


Body Tumors: Therapy response

**Neuroblastoma**
Stage IV Pelvic 14yrs

Baseline
ADC = 0.68

6 Cycles
ADC = 0.68

MIBG therapy
ADC = 1.027

MIBG therapy + new chemo
ADC = 1.682
**Tumors: Whole-body DWI**

- Whole-body DWI, especially DWIBS, has potential to detect mets in solid organs.
- Combination of WB MRI with WB-DWI has potential to replace or complement PET for lymphoma evaluation.
- Promising results in lymphoma staging.
- But few limitations:
  - Lungs
  - Lymph nodes
  - Red marrow

*Littooij AS et al. Eur Radiol 2014; 24:1153-65*

@ Littooij A, et al. JMRI 2015; 42:1646-55

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**Bowel Imaging: Detection of inflammation**

- DWI can be used in 3 ways in inflammatory bowel disease:
  - **1. detection of inflammation**
  - **2. detection of associated lymph nodes**
  - **3. detection of abscess and fistulas.**
**Bowel Imaging: Roles of DWI**

- DWI helps to detect inflammation®
- Good correlation between signs of active inflammation on conventional MRE and diffusion restriction*
- DWI alone not as good as post-Gd imaging for detection of active inflammation but addition of DWI increases accuracy#
- DWI more sensitive for detection of active inflammation than post-Gd imaging$


**Bowel Imaging: Roles of DWI**

- Qualitative and quantitative DWI not as good as conventional MRE to detect clinically active inflammation (wPCDAI and PUCAI)

IBD vs No IBD

<table>
<thead>
<tr>
<th>AUC</th>
<th>Sensitivity</th>
<th>1-Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.84</td>
<td>0.50</td>
<td>0.93</td>
</tr>
<tr>
<td>0.79</td>
<td>0.50</td>
<td>0.85</td>
</tr>
<tr>
<td>0.74</td>
<td>0.50</td>
<td>0.81</td>
</tr>
</tbody>
</table>

Active IBD vs No activity

<table>
<thead>
<tr>
<th>AUC</th>
<th>Sensitivity</th>
<th>1-Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.72</td>
<td>0.46</td>
<td>0.97</td>
</tr>
<tr>
<td>0.50</td>
<td>0.50</td>
<td>0.83</td>
</tr>
<tr>
<td>0.46</td>
<td>0.50</td>
<td>0.81</td>
</tr>
</tbody>
</table>

Alsabban Z et al. Clinical Imaging 2017; 41:14-22
Bowel Imaging: pitfalls

- Terminal ileum can normally be slightly bright on DWI!
- Artifacts from fecal loading

Bowel Imaging: Roles of DWI

- Overall, DWI adds little over conventional MRE due to poor specificity and pitfalls
- May have value when Gad cannot be injected
Other applications

- Pelvic inflammatory disease in teenage girls.
- To find gonads in disorder of sex development (DSD) with ambiguous genitalia.
- To find ovaries in cases with pelvic mass and abdominal testes in undescended testes\textsuperscript{51}.

**Summary**

- DWI good complementary sequence for detection
- Helps in characterization of lesions like tumor and abscess
- Not yet robust for staging and therapy response assessment
Summary

- Quantitative DWI holds great promise as biomarker but needs standardization of technique!
- Interesting to see what other models like IVIM play.

Thank you