TOWARDS A DEFINITION OF « OBSTRUCTION » ?

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ISCORN 2010
Congenital Urine Flow Impairment (CUFI) & antenatal diagnosis

- Incidence: 0.2-2% pregnancies
- Uropathies: 17% of all antenatal pathologies
- Pyelo Ureteric Junction (PUJ) anomaly: 1/800 preg.
  - 20% CUFI are diagnosed before 24 wks of gestation
GOSH 1980 – 2002
3800 antenatal diagnosis

- PUJ: 50%
- Reflux: 15%
- Duplication: 10%
- DMK: 10%
- Megaureter: 9%
- Valves: 4%
- Misc.: 2%

H.K. Dhillon, I. Gordon, P.G. Ransley
Before birth: 4 sources of information

- U/S scan
- Urine + cord blood biochemistry
- MRI scan
- Longitudinal follow-up
Antenatal U/S scan

- Urinary tract dilatation
- Nb & position of the kidneys
- Parenchymal echogenicity
- Bladder
- Amniotic fluid

Photo: J.P. Pracros
Dilatation

- Male to female sex ratio: 2:1
- Classification of the Society of Fetal Urology
- Anteroposterior renal pelvis diameter: No consensus
  - > 5 mm before 25 wks
  - > 10 mm after 25 wks
  - For others: > 7mm in the 3rd term
### Table 3: Estimated breakdown of ANH by severity.

<table>
<thead>
<tr>
<th>Severity</th>
<th>&lt;10 mm</th>
<th>&gt;10 mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>56.7–69</td>
<td>12.5–29.8</td>
</tr>
<tr>
<td>Moderate</td>
<td></td>
<td>1.3–13.4</td>
</tr>
<tr>
<td>Severe</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Ahmad and Green (2005) [20,24].
Interpretation of dilatation

- Physiology: Slow canalization of the excretory system
- Transient CUFI ++++++
- Permanent CUFI
- Vesico-ureteral reflux
- Structural anomalies (Prune-Belly, Collagene anomalies)
Slow canalization of the urinary tract

- Nephronic construction: 9 - 36 wks
- Slow canalization of the ureters
- Maturation of the excretory system continues beyond 36 wk and birth
- Late histological connections between bladder and posterior urethra (25 wk)
Construction of the fetal urinary tract
Duplex in a 21 wk old embryo
Fetal urine transit

- How does urine flow from the kidneys to the bladder during the first part of gestation?
- **Suffusion** (positive gradient)?
- Role of urachus?
Transient CUFI +++

- Delayed connections between embryonic structures or abnormal division of embryonic structures
  - Division of the ureteric bud: PUJ
  - Connection ureter - bladder: UVJ
  - Connection bladder – urethra: VUJ
- Dilatation is a sequela of a past event
Vulnerable zones

- Zones of confluence or division of the various embryonic structures
- PUJ: Wolf
- UVJ: Wolf + UGS
- VUJ: Wolf + Muller
Table 6: Incidence of ANH resolution during the 3rd trimester and after birth.

<table>
<thead>
<tr>
<th>Author</th>
<th>3rd trimester</th>
<th>After birth</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liaw, et al.</td>
<td>&gt;10 (&gt;23 wks)</td>
<td>64%</td>
</tr>
<tr>
<td>Corević, et al.</td>
<td>&gt;4 (&gt;32 wks)</td>
<td>33%</td>
</tr>
<tr>
<td>Mendel, et al.</td>
<td>&gt;8 (&gt;20 wks)</td>
<td>55%</td>
</tr>
<tr>
<td>Hefting, et al.</td>
<td>&gt;8 (&gt;15 wks)</td>
<td>50%</td>
</tr>
<tr>
<td>Padévin, et al.</td>
<td>&gt;4 (&lt;24 wks)</td>
<td>56%</td>
</tr>
<tr>
<td>North, et al.</td>
<td>&gt;8 (&lt;30 wks)</td>
<td>45%</td>
</tr>
<tr>
<td>Steck, et al.</td>
<td>&gt;4 (&lt;22 wks)</td>
<td>28%</td>
</tr>
<tr>
<td>Stempak, et al.</td>
<td>&gt;7 (&gt;31 wks)</td>
<td>30%</td>
</tr>
<tr>
<td>Zhang, et al.</td>
<td>4-10 (&gt;22 wks)</td>
<td>34%</td>
</tr>
<tr>
<td>Secker, et al.</td>
<td>&gt;5 (16-26 wks)</td>
<td>55%</td>
</tr>
<tr>
<td>Jawo, et al.</td>
<td>&gt;10 (&gt;28 wks)</td>
<td>66%</td>
</tr>
<tr>
<td>Signorelli, et al.</td>
<td>4-10 (&gt;25 wks)</td>
<td>56%</td>
</tr>
</tbody>
</table>

Journal of Pediatric Urology – June 2010
Permanent CUFI

- Documented after birth
  - PUJ anomalies
  - UVJ anomalies (megaureter, duplication ±ureterocele
  - PUV
- MORPHOLOGICAL investigations
  - Dilatation
- FUNCTIONAL investigations
Permanent CUFI - PUJ
Permanent CUFI - UVJ
Ultrasound

Amniotic fluid

- Subjective evaluation of the quantity of AF
- Oligohydramnios
  - AF circulation
  - AF turn over
- Polyhydramnios
Prenatal MRI

- Place to be defined
- MRI + Gd-DTPA: No approval in fetus
The place of prenatal MRI

Photos: JP Pracros, L Guibaud
### Biochemistry

**Fetal urine and fetal blood biochemistry**

« Dysplasia »

<table>
<thead>
<tr>
<th>Component</th>
<th>% Sensibility</th>
<th>% Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na+ (75-100mg/dl)</td>
<td>56-87</td>
<td>64-80</td>
</tr>
<tr>
<td>Ca++ (8mg/dl)</td>
<td>100</td>
<td>27-60</td>
</tr>
<tr>
<td>β2 microglobuline (&lt;4mg/dl)</td>
<td>17-80</td>
<td>22-36</td>
</tr>
<tr>
<td>Osmolarity (&lt;200 mOsm/l)</td>
<td>70-83</td>
<td>75-82</td>
</tr>
<tr>
<td>β2 microglobuline blood</td>
<td>66</td>
<td>100</td>
</tr>
</tbody>
</table>

Françoise Muller
Biochemistry

- Poor prognosis factors
  - Na+ > 100 mg/dl
  - Cl- > 90 mg/dl
  - Osmolarity > 200 mOsm/l
  - Urine β2 microglobuline > 6 mg/dl
  - Total proteins > 40 mg/dl
  - Blood β2 microglobuline > 5 mg/l
Biochemistry of fetal urine

- Do electrolytes in fetal urine reflect fetal renal function?
- What is the role of the fetal kidney in the fetal dialysis?
<table>
<thead>
<tr>
<th>Mother</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placenta &amp; membranes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fetal blood circulation</td>
</tr>
<tr>
<td>= low Renal Blood Flow</td>
</tr>
<tr>
<td>= low GFR / TF</td>
</tr>
</tbody>
</table>

RBF / Unit mass = constant

High vascular resistance patterns
80 ml/mn
250 ml/mn
What can we learn from experimental works?

- **In the fetal animal model:**
  - Early obstruction of the urinary tract causes structural lesions of the renal parenchyma
  - Late obstruction causes dilatation

- **In the mature animal model**
  - Dilatation of the urinary tract
  - Durable obstruction causes renal atrophy
    - Ipsilateral loss of kidney weight
    - Contralateral gain of kidney weight: renal dialogue
Ureteral obstruction in the fetal lamb
Histopathology of obstruction

- Tissular infiltration with macrophages (TGF β1) = fibrosis
- Collagen I, III, V in the interstitium
- Collagen IV in the basal membranes

= **Non-specific response also found in stenosis of the renal artery**
Modification of function

- Ultimate response to significant UFI:
  - Reduction of ipsilateral function \((GFR = RBF \text{ and TF})\)
  - Increased contralateral renal function \((GFR = RBF)\)
- How does UFI affect GFR?
- How do the kidneys exchange information?
Renal blood flow

- No UFI: Equal renal blood flow
- % cardiac output
- Unilateral UFI: Reduced ipsilateral renal blood flow, increased contralateral blood flow
- Bilateral UFI: Reduced ipsilateral and contralateral renal blood flow, % cardiac output absolute parameter
Mediators

- **Significant UFI** = Reduction of RBF
- Mediators:
  - Endothelium-derived relaxing factors (NO)
  - Renin angiotensin
  - Platelet activators
  - Thromboxane A2
  - Increased activity of the sympathetic system

= **RENAL HYPOXIA** (ischaemia of the papilla)
UFI = RENAL ISCHEMIA

- The papilla is the most vulnerable zone for ischaemia
- « Megacalicosis »
The contralateral kidney response to UFI

- **Contralateral renal hypertrophia** if UFI is significant
- Increased contralateral kidney weight / Increased DNA content / Identical nb of glomerules
- **Glomerular hyperfiltration**
  - Short term positive response
  - Long-term negative response (glomerular sclerosis)

Koff
Post natal management

- Confirm diagnosis:
  - **Morphological investigations:** U/S + Cystography + Uro MRI
  - **Functional investigations:** Mag 3 + Uro MRI + (subsequent urodynamic studies)
- Only emergency: PUV
Morphological investigations

- **Post natal U/S scan:**
  - Day 8 – 15
  - Sooner after birth if suspicion of PUV
  - Dilatation pelvis / ureter
  - Parenchyma
  - Kidney position and number
  - Bladder wall
  - Ureterocele
  - Posterior urethra
Predictive U/S criteriae of renal deterioration

- Dilated calyces?
- Increased dilatation $\geq 5$ mm
- (Thinning of the renal parenchyma?)
- (Parenchymal echogenicity?)

= Serial imaging
Morphological investigations

- **Cystography**
  - Controversies (demonization ?)
  - **Agreed indications:**
    - Dilated ureter(s)
    - Thick walled bladder / dilated posterior urethra
    - Ureterocele / Duplex
  - **Discussed indications**
    - Dilated pelvis(es) without dilated ureters
    - Antenatal dilatation / No post natal dilatation
Direct cystography

ML Godley, PG Ransley, I. Gordon

Isotopic cystography

JP Pracros Contrast cystography
Top-Down approach

- Cystography performed (to detect VUR) only if DMSA is abnormal

  
  
  
  
Indirect cystography

- Indirect Mag3 cystography: Low sensitivity to detect reflux
Should we perform a cystography in a newborn with a history of antenatal U.T. dilatation?

- **Yes**
  - 15-30% are refluxers
  - This is the only way to exclude valves in boys (4%) which require urgent treatment
  - It may lead to antibioprophylaxis / circ.
  - It is a safe investigation when performed by a paediatric radiologist
  - U/S is a poor investigation to detect reflux

- **No**
  - It is painful and unpleasant
  - It has a significant morbidity (1% UTI)
  - Radiations ++
  - Diagnosing reflux is unnecessary in a asymptomatic child
  - There is no scientific evidence that antibioprophylaxis is helpful to reduce UTI and renal scars
Functional studies
Which isotope study?

- **Mag 3** for most **BUT**
- **Post-diuretic curves**, sequential images or the **T 1/2** are often **insufficient** to define impaired drainage.
- Our current knowledge suggests that there is **no straightforward relation** between the quality of drainage and the risk of functional deterioration.
- Poor drainage with unaltered split function should not lead to surgery per se.
DMSA vs. Mag 3

- Isotope studies: Which isotope should we use in babies with an antenatal history of UT dilatation?

- Difficulties of interpretation of the drainage curves in dynamic studies (DTPA / Mag 3):
  - Child’s hydration
  - Child’s position (gravity)
  - Bladder fulness
  - Overall GFR

- Should we only request DMSA studies as relative function is the only reliable criteria to establish whether a dilatation is significant or not?

- Serial scans
To drain or not to drain
Limits of interpretation of the drainage curves with Mag 3 scan

Capacity vs. outflow
Capacious system with a slow drainage or obstructed system
Current views

- From a nuclear medicine aspect, it is only deterioration on sequential studies that is an indication for surgery. Stable function, even if reduced, is an indication to maintain a conservative watchful approach.
Serial isotope studies

- Reduced relative function: Is it the only reliable criteria to define a significant UFI?
- How to interpret relative function? Differential growth between the « good » kidney and the « not so good » kidney?
Other parameters

- $T_\frac{1}{2}$
- Parenchymal thinning
- Parenchymal echogenicity
- Reassessment after nephrostomy

= Not sufficient
Bilateral dilatation

- **Split function is of little value**, unless the drop of split function on one side is associated with a corresponding significant increase in the dilatation on ultrasound on the same side.

- **Surgery on the worst side is often recommended**
Functional MRI

morphology

function
Dynamic functional screening

- Activity curves in the zones of interest
- Intake, wash out curves
MRI and GFR

- Currently, accurate absolute quantification of GFR is not possible with MRI.
MRI before and after pyeloplasty
Obstruction = Ischemia

- Neither isotopic studies nor MRI scan can accurately measure Renal Blood Flow or parenchymal blood flow
- PET scan ?
- Urine Gas ?
Biochemical signature of « obstruction »

- MRI spectroscopy
- « Obstructed » urine contains unidentified molecules which may reflect significant Urine Flow Impairment (UFI)
Renal pelvis urine vs surgical treatment (12 months survey)

Scores Plots:
- Renal pelvis urine, obtained during surgery
- With surgery, 12 months survey

3 components model, $R^2(X)=0.44$ and $Q2(cum)=0.54$

Loading Plots:

Assignment (to be confirmed by 2D NMR experiments):
1: 1.14ppm = α-ketoisovalerate; 2: 1.94ppm = isovalerate; 3: 2.22ppm = adipate,
4: 2.55ppm = α-methylaspartate; 5: 2.68ppm = aspartate; 6: 2.72ppm = dimethylamine;
7: 3.02ppm = α-ketoisovalerate; 8: 3.11ppm = N,N,N-trimethyllysine; 9: 3.27ppm = TMAO;
10: 3.30ppm = β-phenylethylamine; 11: 3.92ppm = inosine-uridine?; 12: 4.02ppm = serine;
13: 4.06ppm = creatinine; 14: 5.25ppm = α-glucose; 15: 5.78ppm = uracil?,
16: 6.65ppm = p-hydroxyphenylpyruvate; 17: 6.91ppm = dopamine; 18: 7.71ppm = indole
Inclusion vs surgical treatment (12 months survey)

Scores Plots:
- Inclusion
- With surgery, 12 months survey

7 components model, R2(X)=0.72 and Q2(cum)=0.22

Loading Plots:

Assignment (to be confirmed by 2D NMR experiments):
1. 1.14ppm = α-ketoisovalerate;
2. 1.82ppm = γ-hydroxybutyrate, spermine;
3. 1.94ppm = isovalerate;
4. 2.22ppm = adipate;
5. 2.55ppm = α-methylaspartate;
6. 2.68ppm = aspartate;
7. 2.95ppm = asparagine, carnosine;
8. 3.02ppm = α-ketoisovalerate;
9. 3.05ppm = creatinine;
10. 3.07ppm = tyrosine;
11. 3.11ppm = β-aminocisobutyrate;
12. 3.17ppm = cis-aconitate;
13. 3.26ppm = indole-3-lactate;
14. 3.30ppm = β-phenylethylamine;
15. 3.77ppm = arginine-glutamate;
16. 3.84ppm = glycyglycine;
17. 3.92ppm = p-hydroxyphenylpyruvate;
18. 4.06ppm = tryptophan;
19. 5.76ppm = uracil;
20. 7.83ppm = kynurenate-hippurate;
Postnatal management

- U/S + isotope follow-up in most CUFIs if:
  - Asymptomatic
  - Stable or improved dilatation (U/S)
  - Stable or improved renal function (Scinti)
- Otherwise surgery is discussed
Longitudinal studies (GOSH)

- Pelvis Ø < 20 mm: very surgical indications
- Pelvis Ø 20 - 30 mm: 31%
- Pelvis Ø 30 - 40 mm: 64%
- Pelvis Ø 40 - 50 mm: 75%
- Pelvis Ø > 50 mm: 100%

= Surgery < 20% patients

H. Dhillon, P.G. Ransley
The concept of « obstacle »

- Renal urodynamic and hemodynamic are closely related
- Renal blood flow:
  - Mag 3
  - MRI Gadolinium DTPA
  - PET scan
- Biochemical signature of UFI
  - Urine MRI spectroscopy
Thank you