HNF1B-related disease:
a paradigm of developmental disorder eligible for ADTKD

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Referral Center for Orphan Renal Diseases
Toulouse - France
Agenda

- Epidemiology
- HNF1B-related nephropathy: a tubulointerstitial disease? pro/con
- How to diagnose HNF1B-related disease?
  - Extra-renal findings
  - Family history
  - Genetic testing is mandatory
- The HNF1B score as a tool for pre-genetic screening
- Specific management
  - Electrolyte disorders
  - Transplantation in HNF-1 related disease
  - Genetic counselling
Prevalence of HNF-1B disease: study cohorts of >50 patients with renal presentation and/or MODY

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>N. Studies</td>
<td>2</td>
<td>4</td>
<td>3</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>N. Subjects</td>
<td>165</td>
<td>343</td>
<td>587</td>
<td>749/650 fam</td>
<td>?</td>
</tr>
<tr>
<td>N. HNF1B (%)</td>
<td>30 (18%)</td>
<td>57 (17%)</td>
<td>118 (20%)</td>
<td>6</td>
<td>-</td>
</tr>
</tbody>
</table>

Prevalence of HNF1B disease in general population?

- Areas where pediatric and adult nephrologists have a long-standing interest for HNF1B disease
- To evaluate prevalence in two independent areas (internal control)
- To estimate simultaneously the prevalence of others orphan renal diseases (Alport syndrome, Fabry disease and nephronophthisis) (external control)
Prevalence of HNF1B in general population?

Identification of cases
1) All Renal Units
2) Regional Registries for Rare Renal Diseases & Renal Transplantation
3) Genetic Lab

Inclusion criteria
• Being a permanent resident in the studied regions
• Established diagnosis of one of the 4 diseases (biochemistry, pathology or genetic test)
Prevalence of HNF-1B disease: descriptive epidemiology in South-West of France, and comparison to rare inherited renal disorders

| Area                | Midi Pyrénées | Limousin | All | Prevalence (pmh) South-West France | Other studies |
|---------------------|---------------|----------|-----|-----------------------------------|---------------
| N. Inhabitants (INSEE, 2010) | 2,929 M | 0,746 | 3,675 |                                   |               |
| N. diagnosed       |               |          |     |                                   |               |
| Alport              | 47            | 8        | 55  | 15                                | 19-25         |
| Fabry              | 10            | 3        | 13  | 3.7                               | ≈4.0          |
| Nephronophthisis   | 15            | 2        | 17  | 4.6                               | ?             |
| HNF1B              | 43            | 12       | 55  | **15**                            | ?             |

*Chambaraud et al, in preparation*
Limitations

This figure likely is an underestimation

- Ascertainment bias (kidney, not diabetes-MODY)

- Undiagnosed cases (wide variability and mild phenotype in adults)
Renal involvement in HNF1B disease

Most frequently affected target-organ

Almost complete penetrance, if correctly detected

Extreme variability among and within families
I-3, born 1956
2006: S creat 119, GFR 60
Poor corticomedullary differentiation
Few renal cysts, bilateral
No reflux
Hypokalemia 3,2 - Ku = 50/d
Magnesium: 0,52
Proteinuria 0,1g/d
No diabetes mellitus
1 liver cyst

II-1
« Polycystic »
kidney disease

II-2, born 1977
Neonatal RHD + reflux
Right Nx 1978
ESRD 1999 K+ = 2,6
No diabetes

II-3, born 1979
S creat 140, GFR 65
Single left kidney, and cysts

HNF1B point mutation
« ... the renal phenotype in adults with HNF1B disease is clearly one of chronic tubulointerstitial nephritis... »

Faguer S et al, Kidney Int 2011, 80, 7:768-76

27 adults from 20 families, median age at last FU = 35 years (16-74)

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematuria</td>
<td>0</td>
</tr>
<tr>
<td>No proteinuria</td>
<td>74%</td>
</tr>
<tr>
<td>Low-grade proteinuria (&lt;1 g/d)</td>
<td>26%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>7%</td>
</tr>
</tbody>
</table>

Polyuria was not a finding
« ... and slowly progressive kidney failure »

Faguer S et al, Kidney Int 2011, 80, 7:768-76

median yearly eGFR decline:
-2.45 mL/mn/1.73m²/yr
In addition, in adults with HNF1B disease, additional features point to defective tubular transport

Faguer S et al, Kidney Int 2011, 80, 7:768-76

• Tubular leak of either of 2 cations is a very suggestive finding
  • Hypomagnesaemia (Mg\(^{++}\) < 0.75 mmol/l) in 62%
    resulting from renal wasting (FE\(_{Mg}\): 7-22 %, N<0.5%)

• Hypokalaemia (< 3.5 mmol/L) in 46%
  Despite renal decline: 10 individuals with CKD 3-5 had K\(^{+}\) < 3.5 mmol/L
  1 patient started on dialysis with K\(^{+}\) = 2.6 mmol/L

→ hypokalemia or hypomagnesemia were detected in 15 patients (62%)

• 2 unrelated patients presented with generalized defects of proximal and distal tubular function
Hypomagnesemia (< 0.65 mmol/L) is a frequent finding in children with HNF1b disease

... and is related to renal leak

*Adalat S et al. JASN 2009;20:1123-1131*

Fractional magnesium excretion = 6.5%
(4.5-14.3, N< 4%)
Target genes HNF1B (2012)?

<table>
<thead>
<tr>
<th>Tubulogenèse</th>
<th>Différenciation néphronique</th>
<th>Homéostasie epithéliale &amp; transport tubulaire</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Socs3</strong></td>
<td><strong>Umod</strong></td>
<td><strong>Fxyd2°</strong></td>
</tr>
<tr>
<td><strong>Pax2</strong></td>
<td><strong>Pkhd1</strong></td>
<td><strong>Kif12</strong></td>
</tr>
<tr>
<td><strong>LHX1</strong></td>
<td><strong>Pkd2</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Wnt9b</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

°gène cible chez l’homme
Homodimère (ou hétérodimère HNF-1α/HNF-1β)
However, some aspects are disputable for typical TKD

1. Small sized kidneys is not a frequent finding

2. Renal pathology is equivocal

3. (Unexplained acute kidney deterioration may occur (3/27, 11%)

4. (in contrast to UMOD and MUC1 diseases, but alike REN disease, renal involvement in HNF1B is not restricted to adulthood)
Renal imaging in *HNF1B* adult patients
Renal imaging (24/27 individuals) demonstrates extreme heterogeneity and escapes easy classification

_Faguer S et al, Kidney Int 2011, 80, 7:768-76_

**Kidney size at last FU**

<table>
<thead>
<tr>
<th>Size Type</th>
<th>Count (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>13 (61%)</td>
</tr>
<tr>
<td>Small bilateral</td>
<td>5</td>
</tr>
<tr>
<td>Small unilateral</td>
<td>2</td>
</tr>
<tr>
<td>Massively enlarged</td>
<td>2 (9%)</td>
</tr>
<tr>
<td>Small unilateral</td>
<td>7 (30%)</td>
</tr>
</tbody>
</table>

A cystic disease? Not a universal finding - possible overlap

- **Normal kidney**: 12% normal size and shape, no cyst
- **Renal cysts**: 62%, the majority with few (≤ 5) cortical or medullary cysts per kidney
- **Solitary kidney**: 21%
- **Diverse abnormalities**: 16% (nephrocalcinosis, kidney stone, hydronephrosis or hydroureter, and vesicoureteric reflux)

9 patients (38%) had no detectable renal cyst between age 16 and 48 in 6 cystic pts with sequential imaging, no progressive increase of cysts number
To summarize renal imaging in young adults with HNF1B disease

- ≈ 60% have normal sized kidneys with regular shape, ≈ 60% harbor a small number of bilateral renal cysts
- Imaging studies is not a diagnostic clue for HNF1B disease but is mandatory to rule out
  - ADPKD/ARPKD
  - obstructive uropathy (irregular shape)

Additional imaging studies at older age would be useful
# Renal phenotype in children with HNF1b disease

## Imaging (N= 21)$^2$

<table>
<thead>
<tr>
<th>Condition</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilateral disease</td>
<td>76%</td>
</tr>
<tr>
<td>Large K, echogenic, no cyst</td>
<td>43%</td>
</tr>
<tr>
<td>Large K, echogenic, with cysts</td>
<td>24%</td>
</tr>
<tr>
<td>Hydronephrosis</td>
<td>14%</td>
</tr>
<tr>
<td>Unilateral MCKD</td>
<td>19%</td>
</tr>
</tbody>
</table>

**Uncommon** $^1$-$^2$

<table>
<thead>
<tr>
<th>Condition</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single kidney</td>
<td>≈5%</td>
</tr>
<tr>
<td>Normal US</td>
<td>&lt;5%</td>
</tr>
</tbody>
</table>

## Clinic findings at last FU

<table>
<thead>
<tr>
<th></th>
<th>Adalat</th>
<th>Heidet</th>
</tr>
</thead>
<tbody>
<tr>
<td>N.</td>
<td>21</td>
<td>75</td>
</tr>
<tr>
<td>Age</td>
<td>8.0 yr</td>
<td>8.5 yr</td>
</tr>
<tr>
<td>Early gout</td>
<td>?</td>
<td>5%</td>
</tr>
<tr>
<td>eGFR $&gt;$ 80</td>
<td>63 (8-113)</td>
<td>?</td>
</tr>
<tr>
<td>CKD stage 5</td>
<td>2 (21%)</td>
<td>?</td>
</tr>
<tr>
<td>ESRD</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

$^1$Heidet & Decramer, CJASN 2010, 5:1079

$^2$Adalat S, JASN 2009, 20:1123
Renal course in childhood: data from 43 individuals - no sequential study

<table>
<thead>
<tr>
<th>Series</th>
<th>Toulouse(^1)</th>
<th>France(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N.</td>
<td>18</td>
<td>25</td>
</tr>
<tr>
<td>Age at diagnosis</td>
<td>Antenatally</td>
<td>6</td>
</tr>
<tr>
<td>Median FU (years)</td>
<td>7 (39%)</td>
<td>2.5</td>
</tr>
<tr>
<td>GFR at last FU</td>
<td>14 (56%)</td>
<td></td>
</tr>
<tr>
<td>&gt; 80</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>&gt; 70</td>
<td>7 (39%)</td>
<td>-</td>
</tr>
<tr>
<td>40-80</td>
<td>10 (40%)</td>
<td></td>
</tr>
<tr>
<td>40-70</td>
<td>8 (45%)</td>
<td>-</td>
</tr>
<tr>
<td>&lt; 40</td>
<td>2 (10%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>ESRD</td>
<td>1 (5%)</td>
<td>0</td>
</tr>
</tbody>
</table>

\(^1\) Decramer S, J Am Soc Nephrol, 2007
However, some aspects are disputable for typical TKD

1. Small sized kidneys is not a universal finding

2. Renal pathology is equivocal in HNF1B-disease

3. Unexplained acute kidney deterioration may occur (3/27, 11%)

4. (in contrast to UMOD and MUC1 diseases, but alike REN disease, renal involvement in HNF1B is not restricted to adulthood)
Renal pathology: is HNF1B-disease really a tubulointerstitial nephritis?

1. Very few data
   - Practical reasons: small or cystic kidneys = risk of complication
   - So far, diagnostic value not established

2. ≈ 20 individual reports in the literature, mostly in children (or fetus)
   - Glomerulocystic disease (n=6)
   - Oligomeganephronia (n=3)
   - Cystic renal dysplasia (n=2)

3. Tubulointerstitial findings
   - No specific assessment
   - Neither TBM lamellation, nor increased width
   - No specific study of HNF1B by IHC

Madariaga, CJASN, 2013
Pathological findings on kidney biopsy in 6 adults with HNF-1B mutation
Bellanné, Chauveau et al., Ann Intern Med 2004

- Enlarged glomeruli 4/6
- Glomerular cysts 2/6
- Oligomeganephronia 1/6

None is specific

- Interstitial fibrosis 6/6
- Diabetic GN 0/6
As compared to *UMOD* nephropathy

- Due to scarce data, renal pathology is still of limited value to diagnose HNF1B-related disease.
- Whether kidney biopsy should be routinely performed in adults with suspected HNF1B-related disease is not yet clear.
- We need to better delineate the pathological characteristics, and to develop biomarkers that could help in establishing the diagnosis of HNF1-related kidney disease, without genetic testing.
What may raise clinical suspicion of HNF1B disease in patients with renal presentation?

1. Extrarenal findings
2. Family history
Extrarenal findings

1. No large cohort, and few data on natural history

2. Target organs
   - Pancreas
   - Liver:
     - fluctuating liver tests in 40-50% of adults – liver biopsy almost normal - long term prognosis unknown (severe worsening post kidney transplant)
     - neonatal jaundice\(^1\)\(^2\) with reduction of intrahepatic bile ducts
   - Genital tract malformations (impaired fertility)
     - Males: epididymes cysts or bilateral absence of vas deferens
     - Females: bicornual uterus, hemiuterus, or uterus and upper vagina aplasia
   - Brain: intellectual impairment with autistic traits\(^3\)
     - Not well established in the spectrum of the disease
     - Only in patients with large deletion of the gene

\(^1\)Roelandt, Hepatology 2012
\(^2\)Beckers J Pediatr 2007
\(^3\)Moreno-DE-Luca D, Am J Hum Genet, 2010
Extrarenal findings

- **Pancreas**
  - Diabetes mellitus (MODY5)
    - β-cell dysfunction and insulin resistance
    - Typically non-obese patients at a median age of 20-30 years, up to >70 years,
    - Clinically overt or detected by screening, or NODAT\(^1\)
    - Course debated
      - exhibits a slowly progressive course with late requirement for insulin therapy\(^2\)
      - or poor response to sulphonylurea\(^3\)
    - (ketoacidosis may occur, in adult\(^4\) or even in teenager\(^2\))
  - Pancreas atrophy is detected in almost half the adult patients (CT) - pancreas exocrine failure should be routinely detected at diagnosis (low faecal elastase)

\(^1\)Zuber, Nat Rev Nephrol
\(^2\)Bellanné, Ann Intern Med 2004
\(^3\)Pearson Diabetes Care 2004
\(^4\)Faguer S, Kidney Int 2011
What may raise clinical suspicion of HNF1B disease in patients with renal presentation?

1. Extrarenal findings

2. Family history with AD

However

- In all series, 50-60% of cases are found to have de novo mutation
- In families with evidence for AD inheritance, wide phenotypic variability
- Phenocopies can be detected by family screening
- Mosaicism (rare)

1 review in Chauveau Nephrol Therap, 2012

3 Yorifuji, J ClinEndocr Metab 2004
Thus, given - the lack of pathognomonic characteristics - and the wide overlap with other conditions, a genetic test is mandatory to diagnose HNF1B disease.
Mutations in *HNF1b*-related disease

- Gene located on 17q12

- Genetic changes
  - 50% point mutations (>50 reported), (missense, false-sense, splice-site mutation, or indel) are mostly private and located in the DNA-binding domain (clusters in exons 2 and 4)
  - 50% micro-chromosomal rearrangement mostly large recurrent deletion of 1.2–1.5Mb - rarely one single exon
  - very low risk of mosaicism

- No genotype-phenotype correlation
- Disease mechanism = haploinsufficiency

Adapted from Heidet L et al. *CJASN* 2010;5:1079-1090
Genetic screening for *HNF1B* mutation

**current approach**

1) Large deletion?

2) If not, sequencing for point mutation

*(Much easier than ADPKD or Alport)*

Cost ≈ 380-780 euros in France
How to improve pre-genetic screening? The HNF1B score

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Item</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family history</td>
<td></td>
<td>+2</td>
</tr>
<tr>
<td>Antenatal renal abnormalities</td>
<td>Uni/bilateral abnormality by renal echography</td>
<td>+2</td>
</tr>
<tr>
<td><strong>Kidneys and urinary tract</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left kidney</td>
<td>Hyperechogenicity</td>
<td>+4</td>
</tr>
<tr>
<td></td>
<td>Renal cysts</td>
<td>+4</td>
</tr>
<tr>
<td></td>
<td>Hypoplasia</td>
<td>+2</td>
</tr>
<tr>
<td></td>
<td>Multicystic and dysplastic kidney</td>
<td>+2</td>
</tr>
<tr>
<td></td>
<td>Urinary tract malformation</td>
<td>+1</td>
</tr>
<tr>
<td></td>
<td>Solitary kidney</td>
<td>+1</td>
</tr>
<tr>
<td>Right kidney</td>
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<td></td>
<td>Solitary kidney</td>
<td>+1</td>
</tr>
<tr>
<td>Electrolyte or uric acid disorders</td>
<td>Low serum Mg²⁺ ((&lt; 0.7 \text{mmol/l})</td>
<td>+2</td>
</tr>
<tr>
<td></td>
<td>Low serum K⁺ ((&lt; 3.5 \text{mmol/l})</td>
<td>+1</td>
</tr>
<tr>
<td></td>
<td>Early-onset gout ((&gt;30 \text{years of age})</td>
<td>+2</td>
</tr>
<tr>
<td>Pathological findings</td>
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<td>+1</td>
</tr>
<tr>
<td>Pancreas</td>
<td>MODY or hypoplasia of tail and neck of the pancreas or pancreatic exocrine insufficiency</td>
<td>+4</td>
</tr>
<tr>
<td>Genital tract</td>
<td>Genital tract abnormality</td>
<td>+4</td>
</tr>
<tr>
<td>Liver</td>
<td>Live test abnormalities of unknown origin</td>
<td>+2</td>
</tr>
</tbody>
</table>
The HNF1B score is a simple tool to select patients for HNF1B gene analysis

Performance of the HNF1B score: ROC curve analysis (433-individual cohort including 56 HNF1B cases)
The HNF1B score is a simple tool to select patients for HNF1B gene analysis

Table 2 | HNF1B score

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<td>Liver</td>
<td>Live test abnormalities of unknown origin</td>
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Figure 2 | Distribution of patients (%) who would be proposed for HNF1B screening according to the HNF1B score (≥8) and to age at genetic screening. X axis shows age ranges (years), and y axis shows percentage of patients with HNF1B score < or ≥8.

Figure 1 | Receiver operating characteristics (ROC) curve of the HNF1B score in a large cohort with HNF1B known status (N = 433), showing the accuracy of the HNF1B score in predicting disease status.
When to screen for HNF1B in patients with renal presentation?

Suspicion of HNF1B disease

Abdominal imaging in parents and clinical exam to rule out ADPKD/ARPKD and renal hypodysplasia (coloboma, BOR syndrome...)

Minimal evaluation for HNF1B disease:
- Family history
- Fasting glucose, liver tests, serum K⁺ and Mg²⁺

HNF1B score

<8
- No genetic testing

≥8
- On FU, if new finding suggestive of HNF1B disease and score ≥ 8
- Consider HNF1B analysis

HNF1B-related disease in a first-degree relative
Specific management in established HNF1B disease in adults

- **Kidney**
  - At presentation: Mg, K, S. creatinine & CT-scan (or MRI)
  - Yearly: Mg, K, S. creatinine - no imaging in the absence of clinical symptom
  - If hypoMg/hypoK: treat only if symptomatic
  - Avoid ACE and ARB
  - ?Screening for chromophobe renal cell carcinoma (2 case reports 37 and 54 years/ bi-allelic invalidation, in addition to germline mutation)

- **Pancreas**
  - At presentation: ?diabetes – fecal elastase
  - Yearly: diabetes FU – fecal elastase if symptom

- **Liver**
  - At presentation and yearly: liver blood tests

- **Genital tract**: only if symptomatic (?)

- **Genetic counselling**
Kidney and combined kidney-pancreas transplantation in HNF-1beta individuals
follow-up in 16 patients from 7 medical Centers

Faguer et al, submitted

• 16 patients (8F, 8M) – 7/16 (44%) large deletion
• Prior Tx:
  – DM in 6/16 (37%), 5 IDDM, mean age at diagnosis 21
  – Liver tests abnormalities in 7 (44%)
  – Exocrine pancreatic failure in 1

• At Tx
  – median age = 27 (5-53)
  – 14 SKT and 2KPT

• FU after 14 SKT
  – Median duration = 69±57 months (4-180)
  – Kidney:
    • Early acute oxalate nephritis n=1
    • Chronic rejection and Re-SKT n=3
  – Severe worsening or de novo abnormal liver tests : 7/14 (50%) – no cirrhosis
  – de novo post-transplant DM : 6/10 (60%), ≈ 3 months post-SKT

- Cytoplasmic calcineurin regulates NFAT (nuclear factor of activated T-cells)
- NFAT are a family of transcription factors expressed in renal, pancreas and liver epithelial cells during development

Hypothesis: could calcineurin inhibitors modify HNF1B expression in epithelial cells?
Lessons from SKT and KPT in HNF-1beta individuals: a plead for dedicated management

- CNI down-regulate HNF1-beta transcriptional activity: *HNF1B* patients are therefore close to bi-allelic inactivation

- Individualized management of ESRF
  - If IDDM or NIDM, consider KTP
    
    *Poitou, Transplant Int 2012 and personal experience*
  
  – In the absence of IDDM/NIDM
    - Test for exocrine pancreatic failure (fecal elastase), and add pancreas enzyme supplementation
    - Inform of the high risk for *de novo* PTDM
    - Minimize CNI exposure and consider prompt withdrawal of steroids
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