MECHANISMS OF RENAL FUNCTION DECLINE AND ESRD

Rémi Salomon
Necker Hospital, Paris, France

Amsterdam, June 17th 2016
Disclosure of Interests

- Alexion (registry, sponsored education)
- Raptor (expert witness, co-investigator)
- Oxthera (co-investigator)

(e.g. employment, consultancy, honoraria, stock ownership, sponsored education, research grant, educational grant, expert witness, other relevant funding, etc ...)
2. Management of renal function decline and ESRD

Q1. How can we optimize a cooperative approach of tertiary expert centers with local care centers, particularly in the patient transition from pediatric to adult care? How/when do we involve non-renal specialists to address extrarenal manifestations?

Q2. Are so-called “renoprotective drugs” dangerous in some rare kidney diseases, such as salt-wasting tubulopathies? Is the generally accepted wisdom in nephrology (such as use of ACE-inhibitors, avoidance of NSAID, etc.) applicable to specific rare diseases and at all levels of kidney function? Are most treatment targets (blood pressure, sodium, dietary protein, etc.) still applicable for this population?

Q3. How should one monitor for potential renal and extrarenal complications and if so, how frequently?

Q4. How can we help the patient and family to accept the chronic disease, live with it and manage it responsibly? Any specific issues related to compliance, monitoring, and follow-up?

Q5. How can we ensure equity of access to optimal care, including expensive drugs?

Q6. What is the optimal modality for dialysis? Does this vary by disorder?

Q7. What is the optimal timing for transplant and role/utility of pre-emptive transplantation? How can we better address the risk of disease recurrence post-transplant?

Q8. What are extrarenal issues in dialysis or transplant settings that call for particular management?

Q9. How can growth-related issues and treatment be optimally managed?
Overview

• 9 questions around management of renal function decline and CKD progression

• Impossible to consider the 150 different rare renal diseases (RRD)

• I choose some examples
  – Our experience
  – The general perspective around RRD

  • Cystinosis in adult
  • *HNF1B* and autism
  • Lowe syndrome/haemorrhage
  • Methylmalonic acidemia/transplantation
  • Growth hormone treatment
Q1. How can we optimize a cooperative approach of tertiary expert centers with local care centers, particularly in the patient transition from pediatric to adult care? How/when do we involve non-renal specialists to address extrarenal manifestations?

Patients with rare disease should be referred to tertiary centre at the time of diagnosis (or for diagnosis to be done) and regularly thereafter.

Adult centre are in general not expert in rare diseases, in each centre it would be wise to have one referent nephrologist with a special interest in rare disease to take care of these patients.

Once a year (or less depending on the situation) a multidisciplinary check-up can be organized during a single day including:

dietician, psychologist, dedicated nurse and the different specialists…
Le réseau de santé des maladies rénales rares de l’enfant et de l’adulte
Acteurs de la filière

- Centre de référence
- Centre de compétences

KDIGO Controversies Conference on Common Elements in Uncommon Kidney Diseases

Séminaire – 14/15.03.2016
2. Les première actions de la filières

www.filiereorkid.com
European networks of reference for rare diseases

- Introduction
- Definition of centre of reference in European countries
- Identifying and designating centres of reference at national level
- Identifying and designating European reference networks
- Diagnosis and care: how can centres of reference best serve rare disease patients?
Transition from pediatric to adult care

Sensibilisation years before

See the adolescent alone during outpatient clinics

Common outpatient clinics (when possible) with both adult and pediatric nephrologists at the time of transition

Edit protocols for the care

Keep talking with the adult nephrologists

Staff with A and P to discuss the cases

Everyone need to know and improve his knowledge about the complications that occur with ageing

Ex: cystinosis
ESRD in cystinosis

Brodin-Sartorius et coll, Kidney Int, 2011
Cystinosis: Hypothyroidism

Brodin-Sartorius et coll, Kidney Int, 2011
Cystinosis: Diabetes

Brodin-Sartorius et coll, Kidney Int, 2011
Cystinosis: neuromuscular complications

Brodin-Sartorius et coll, Kidney Int, 2011
Q2. Are so-called “renoprotective drugs” dangerous in some rare kidney diseases, such as salt-wasting tubulopathies? Is the generally accepted wisdom in nephrology (such as use of ACE-inhibitors, avoidance of NSAID, etc.) applicable to specific rare diseases and at all levels of kidney function? Are most treatment targets (blood pressure, sodium, dietary protein, etc.) still applicable for this population?

Proximal tubulopathies, the albuminuria can be high but there is no evidence that blockade of the RAS is effective, moreover it can be dangerous and not tolerated if dehydration occurs.

NSAID is effective in reducing the amount of urine in tubulopathies, some studies have addressed the question of their toxicity on the long term, what the follow-up should be? DFG measurement? renal biopsies?

Avoid NSAID in tubulopathies in which the natural evolution is chronic renal failure (Dent, Lowe, nephronophtisis …)

Other renoprotective measures:

> blood pressure control under 50 perc
> protein limitation
> lipid and uricemia control
Q3. How should one monitor for potential renal and extrarenal complications and if so, how frequently?

It really depends on the disease and on specific situations, difficult to give general recommendations

....but we can list all the complications that can be encountered (if possible with their frequencies) and guidelines for the care

Some complications are not well known and deserve more collaborative studies

Ex ; **Lowe** and bleeding disorder, **TCF2** and autism (special comments on that)
Renal cysts and diabetes with \textit{HNF1B} mutation or deletion

37 patients de la cohorte HNF1B
   – Centres volontaires
   – Patients vus le temps de l’étude

Vérification de la microdélétion
Evaluation neurolopsychologique
Evaluation morphologique
Comparaison mutation / délétion

Laffargue, Arch Dis Child, 2015
The 17q12 microdeletion syndrome is associated with neurocognitive impairments and microdeletion of the HNF1B gene. A study has been conducted to evaluate the neuropsychological phenotype of patients with this deletion.

**Figure 1**
- **HNF1B deletion**
  - Not schooled (<3 years): 8
  - Normal school progression: 16
  - Schooled: 24

- **HNF1B point mutation**
  - Not schooled (<3 years): 2
  - Normal school progression: 11
  - Schooled: 13

**Figure 2**
- Intellect quotient distribution of patients with HNF1B deletion and point mutation.

**Figure 3**
- Facial phenotypes of patients with 17q12 microdeletion.

**Figure 4**
- Details and results of the study.

**Conclusion**
- We acknowledge that despite the large cohort presented here, our data on neuropsychological phenotype are incomplete as some of the children included in the study were too young to undergo psychological testing.
- Our study shows that all patients with 17q12 microdeletion syndrome have a higher risk of developing neuropsychological disorders such as autism.
- The risk of developing neuropsychological disorders such as autism is higher than in the normal population.
- Our study demonstrates that patients with 17q12 microdeletion syndrome have a higher risk of developing neuropsychological disorders such as autism.

Laffargue et al, Arch Dis Child 2015
Inclus dans cohorte 223

Données cliniques 215

Données "neuro" 175

78.4 %

< 3 ans 26 (14.6%)

≥ 3 ans 149 (85.4%)

Population étudiée

Age moyen : 7.9 ans

Sex Ratio (M/F) : 1.49

V Guigonis (Limoges)
SoRare Ref Centre
26 (14.8%) < 3 ans

4 (2.3 %) Retard de développement

22 (12.6 %) Tout va bien

149 (85.4%) ≥ 3 ans

17 (9.7 %) Développement anormal

2 (1.1 %) Classe adaptée

10 (5.7 %) Institut

1 (0.6 %) Non scolarisé

Scolarité normale

131 (74.8 %) année ± 1

5 (2.9 %) Année = ?
RCAD, *HNF1B* and autism spectrum disorders

- Do have to take into account this association as significant?
- Do we have to consider it for prenatal diagnosis?
- We have certainly to keep in mind this observation in the care
- Do we have to give this information to the families?
Lowe syndrome: a «new» symptom

- Interest of the analysis of a large cohort
- Of digital database
French national Lowe Syndrome network

- Created in 2002 (GIS Maladies Rares, J. Lunardi and R. Salomon)

- 2004-2009: Reinforced by the National Plan for Rare Diseases and creation of Reference Centres
  - Diagnosis
  - Management
  - Epidemiological and clinical research
  - Information and communication

- Different projects including a clinical survey for LS

- Important role of the “ASL” = French LS parents association
Dr G Baujat
Genetic department
Necker, Paris
Lowe syndrome retrospective survey

- Retrospective multicentric review by one physician
- Genetic analysis of OCRL1 (J. Lunardi)
- Medical data: questionnaire
- Phone call to the families for some details (development, visual acuity, education)
- Phenotype-genotype correlations analysis

Average age: 18 years

49 boys from 26 centres in France
Lowe syndrome
Renal manifestations

Constant tubular defect ("Fanconi")

- Diagnosis: ≈ 12 months (26% < 1 m)
- Variable in severity and type ++

1/ acidosis: bicarbonate treatment: 80% (>3.4m)

2/ hypokalemia requiring oral K: 14%

3/ hyperphosphaturia and hypercalciuria 68%
  - fractures 26%, rickets 40%
  - néphrocalcinosis in 58%
Lowe syndrome
Progressive renal function deterioration

KDIGO
Hematological complications

• Isolated microcytosis or microcytic anemia (without iron deficiency): 18

• Bleeding history: notification of 8 cases!
  • Haemorrhagic complications during or after surgery
    – Craniostenosis: 2
    – Scoliosis: 1
    – Cataract surgery: 1
    – Knee surgery: 1
    – Serious bleeding after tooth extraction: 4
  • But few haematoma/ epistaxis
## Preliminary study in 6 LS patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr)</th>
<th>Previous Surgery</th>
<th>Bleeding</th>
<th>PFA-100 Closure Times</th>
<th>von Willebrand</th>
<th>Hb</th>
<th>Fib</th>
<th>Platelets</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>EPI</td>
<td>ADP</td>
<td>Ag</td>
<td>VWF:RCo</td>
<td></td>
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<tr>
<td>1</td>
<td>1</td>
<td>Eye</td>
<td>Yes</td>
<td>85–165</td>
<td>71–118</td>
<td>50–150</td>
<td>50–150</td>
<td>279</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>Neurologic &amp; eye</td>
<td>Yes</td>
<td>&gt;300</td>
<td>166</td>
<td>305</td>
<td>199</td>
<td>9.8</td>
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<tr>
<td>3</td>
<td>5</td>
<td>Eye</td>
<td>No</td>
<td>195</td>
<td>126</td>
<td>295</td>
<td>275</td>
<td>11.7</td>
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<tr>
<td>4</td>
<td>2</td>
<td>Eye</td>
<td>Yes</td>
<td>197</td>
<td>128</td>
<td>251</td>
<td>200</td>
<td>10.1</td>
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<tr>
<td>5</td>
<td>17</td>
<td>Tooth extraction</td>
<td>No</td>
<td>&gt;300</td>
<td>129</td>
<td>262</td>
<td>200</td>
<td>11.7</td>
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<tr>
<td>6</td>
<td>14</td>
<td>Tooth extraction</td>
<td>Yes</td>
<td>189</td>
<td>188</td>
<td>332</td>
<td>224</td>
<td>11.3</td>
</tr>
</tbody>
</table>

>> Platelet dysfunction

Lasne et al, Br J Haematol. 2010
Another way to increase our knowledge on rare diseases: Biomedical Data Warehouse

Nicolas Garcelon (Imagine Institute)

From Individual memory to collective memory organized and sustainable

KDIGO
Necker – Enfants Malades Hospital since ≈ 2000 (essentially 2007)
Number of patients: 366,000 patients
Number of documents: 2,700,000 health records (free text)
Rechercher des patients

Sur tout l'entrepôt

lowe

41/41

Etendre aux synonymes :

+ Ajouter un filtre Full text
+ Ajouter un filtre structuré
+ Filtre patient

41 Patients
498 Documents

Documents contenant 'lowe', en excluant les négations

Refaire une recherche sur le résultat :

Exporter les patients :

Filtrer le résultat ci-dessous :

ok  annuler
 KDIGO

<table>
<thead>
<tr>
<th>Concepts</th>
<th>Nb patients</th>
<th>% résultat</th>
<th>% entrepôt</th>
<th>% résultat / entrepôt</th>
</tr>
</thead>
<tbody>
<tr>
<td>Syndrome de Lowe</td>
<td>36</td>
<td>87.8</td>
<td>0</td>
<td>100</td>
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<tr>
<td>Cataracte</td>
<td>20</td>
<td>48.8</td>
<td>.9</td>
<td>.7</td>
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<tr>
<td>Proteinurie</td>
<td>20</td>
<td>48.8</td>
<td>4.7</td>
<td>.1</td>
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<tr>
<td>Renal</td>
<td>19</td>
<td>46.3</td>
<td>18.6</td>
<td>0</td>
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<tr>
<td>Nephrocalcinose</td>
<td>14</td>
<td>34.1</td>
<td>.2</td>
<td>2.4</td>
</tr>
<tr>
<td>HYPOTONIE</td>
<td>14</td>
<td>34.1</td>
<td>3.5</td>
<td>.1</td>
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<tr>
<td>Hypercalciurie</td>
<td>12</td>
<td>29.3</td>
<td>.2</td>
<td>1.7</td>
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<tr>
<td>Deshydratation</td>
<td>11</td>
<td>26.8</td>
<td>1.1</td>
<td>.3</td>
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<td>Incontinence</td>
<td>19</td>
<td>42.3</td>
<td>4.2</td>
<td>2.1</td>
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<tr>
<td>Constipation</td>
<td>15</td>
<td>42.1</td>
<td>.9</td>
<td>.6</td>
</tr>
<tr>
<td>Fatigue</td>
<td>19</td>
<td>46.3</td>
<td>18.6</td>
<td>0</td>
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<tr>
<td>Anorexie</td>
<td>21</td>
<td>52.4</td>
<td>.7</td>
<td>.3</td>
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</tbody>
</table>
% patients dans le résultat / % patients dans entrepôt

- Syndrome de Lowe (36)
- Cataracte (20)
- Proteinurie (20)
- renal (19)
- Néphrocalcinose (14)
- HYPOTONIE (14)
- Hypercalcurie (12)
- Deshydratation (11)
- CATARACTE CONGENITALE (10)
- Retard de croissance (10)
- Insuffisance renale (10)
- Masse (10)
- Scoliose (10)
- Anémie (9)
- Agitation (9)
- affection (9)
- Constipation (8)
- Glaucome (8)
- Microalbuminurie (8)
- Retard psychomoteur (8)
- Tension (8)
- Albuminurie (7)
- Kyste (7)
- allergie (7)
- Urgences (7)
- Rachitisme (7)
- Crise (7)
- Deminéralisation (7)
- Cyphose (7)
- Acidose (6)
- Tolerance (6)
- baisse (6)
- Douleur (6)
- vesicule (5)
- ectopie testiculaire (5)
- Diarrhee (5)
<table>
<thead>
<tr>
<th>Concepts</th>
<th>Nb patients</th>
<th>% résultat</th>
<th>% entrepôt</th>
<th>% reste</th>
</tr>
</thead>
<tbody>
<tr>
<td>troubles de l'hémostase</td>
<td>5</td>
<td>12.2</td>
<td>0.7</td>
<td>0.2</td>
</tr>
<tr>
<td>Hémorragie</td>
<td>3</td>
<td>7.3</td>
<td>9.9</td>
<td>0</td>
</tr>
<tr>
<td>Hémolyse</td>
<td>2</td>
<td>4.9</td>
<td>0.9</td>
<td>0.1</td>
</tr>
<tr>
<td>Hémophilie</td>
<td>1</td>
<td>2.4</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>Syndrome hémorragique</td>
<td>1</td>
<td>2.4</td>
<td>0.9</td>
<td>0</td>
</tr>
<tr>
<td>Hémolyse intra-vasculaire</td>
<td>1</td>
<td>2.4</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>troubles hémorragiques</td>
<td>1</td>
<td>2.4</td>
<td>1.6</td>
<td>0</td>
</tr>
</tbody>
</table>

Showing 1 to 7 of 7 entries (filtered from 415 total entries)
How can we help the patient and family to accept the chronic disease, live with it and manage it responsibly? Any specific issues related to compliance, monitoring, and follow-up?

Association of patients

Meeting with families and doctors and other professional implicated in the care

Explain the disease to the adolescent (or before)

Dedicated nurses

Psychologist, psychiatrist, psychomotrician ...

Documentation

Specific devices to improve compliance (telemedicine)
Q5. How can we ensure equity of access to optimal care, including expensive drugs?
Disclosure of Interests

• Alexion (registery, sponsored education)
• Raptor (expert witness, co-investigator)
• Oxthera (co-investigator)

(e.g. employment, consultancy, honoraria, stock ownership, sponsored education, research grant, educational grant, expert witness, other relevant funding, etc ...)

KDIGO Controversies Conference on Common Elements in Uncommon Kidney Diseases
June 16 - 19, 2016 | Amsterdam, Netherlands
Q5. How can we ensure equity of access to optimal care, including expensive drugs?
Q5. How can we ensure equity of access to optimal care, including expensive drugs?
Q6. What is the optimal modality for dialysis? Does this vary by disorder?

It depends on the disease

Specific question for hyperoxaluria, methylmalonic acidemia

The size of the patient
Probably PD when the child has severe mental retardation
But need a strong familial involvement (not always possible)
Q7. What is the optimal timing for transplant and role/utility of pre-emptive transplantation? How can we better address the risk of disease recurrence post-transplant?

**Timing of transplantation:**

Is transplantation always possible? Acceptable? Ethical issues...

If one consider that transplantation should not be done, what’s about dialysis?
Sustaining life or prolonging dying? Appropriate choice of conservative care for children in end-stage renal disease: an ethical framework

Janis M. Dionne · Lori d’Agincourt-Canning

Pediatr Nephrol 2014

Table 1 Summary recommendations for shared decision-making regarding the withholding and withdrawing of dialysis in pediatric practice

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommendation 1</td>
<td>Develop a patient–physician relationship that promotes family-centered shared decision-making for all pediatric patients with AKI, CKD, and ESRD.</td>
</tr>
<tr>
<td>Recommendation 2</td>
<td>Fully inform patients with AKI, stage 4 or stage 5 CKD, or ESRD and their parents about the diagnosis, prognosis, and all appropriate treatment options. Inform children and adolescents in a developmentally appropriate manner, and if feasible, seek their assent about treatment decisions.</td>
</tr>
<tr>
<td>Recommendation 3</td>
<td>Facilitate informed decisions about dialysis for pediatric patients with AKI, CKD, or ESRD, discuss prognosis, potential complications, and quality of life with the patient, parents and/or legal guardian.</td>
</tr>
<tr>
<td>Recommendation 4</td>
<td>Establish a systematic due process approach for conflict resolution if disagreements occur about dialysis decisions. Use conflict resolution interventions when family members disagree with one another, when children disagree with their parents, when families disagree with the health care team, or when the health care team disagrees about initiating, not initiating, or withdrawing dialysis</td>
</tr>
<tr>
<td>Recommendation 5</td>
<td>Institute family-centered advance care planning for children and adolescents with AKI, CKD, and ESRD. The plan should establish treatment goals based on a child’s medical condition and prognosis.</td>
</tr>
<tr>
<td>Recommendation 6</td>
<td>Forgo dialysis if initiating or continuing dialysis is deemed to be harmful, of no benefit, or merely prolongs a child’s dying process. The decision to forgo dialysis must be made in consultation with the child’s parents. Give children and adolescents the opportunity to participate in the decision to forgo dialysis to the extent that their developmental abilities and health status allow.</td>
</tr>
<tr>
<td>Recommendation 7</td>
<td>Consider forgoing dialysis in a patient with a terminal illness whose long-term prognosis is poor if the patient and family are in agreement with the physician that dialysis would not be of benefit or the burdens would outweigh the benefit.</td>
</tr>
<tr>
<td>Recommendation 8</td>
<td>Consider the use of a time-limited trial of dialysis in neonates, infants, children, and adolescents with AKI or ESRD to allow for the assessment of extent of recovery from an underlying disorder</td>
</tr>
<tr>
<td>Recommendation 9</td>
<td>Develop a palliative care plan for all pediatric patients with ESRD from the time of diagnosis and for children with AKI who forgo dialysis. The development of a palliative care plan is a continuation of the process of advance care planning and should be family-centered.</td>
</tr>
</tbody>
</table>
Q7. What is the optimal timing for transplant and role/utility of pre-emptive transplantation? How can we better address the risk of disease recurrence post-transplant?

**Timing of transplantation:**

Is transplantation always possible? Acceptable? Ethical issues...

If one consider that transplantation should not be done, what’s about dialysis?

Pre-emptive whenever possible and particularly if dialysis is hazardous or not efficient enough: MMA, hyperoxaluria
**METHYL- MALONIC ACIDEMIA**

- Isoleucine
- Valine
- Méthionine
- Thréonine
- AGNIC...

**Propionyl-CoA**

- **Propionyl-CoA Carboxylase**
- **Méthylmalonyl-CoA racémase**
- **Méthylmalonyl-CoA mutase**

**Acidurie propionique**

**Acidurie méthylmalonique**

- **Succinyl-CoA**
- **NADPH**

**Cycle de Krebs**

**B8 = Biotine**

**B12 = Cobalamine**

KDIGO Controversies Conference on Common Elements in Uncommon Kidney Diseases

June 16 - 19, 2016   |   Amsterdam, Netherlands
Methylmalonic acidemia

- methylmalonyl-coenzyme A mutase deficiency
  - Mut 0 : no activity
  - Mut - : partial activity

- Presentation: coma (intoxication), acidocetosis, hyperammoniemia

- Treatment: low protein intake, carnitine, antibiotherapy to control intestinal flora

- Complications:
  - Neurological
  - Renal
  - Pancytopenia
  - Growth retardation
Renal disease

- Usual complication of the disease despite treatment
  - 47%
  - CRF at 6.5 years (1.5-18.6)
  - More earlier and severe with Mut 0

- Tubulo-interstitial nephritis

- Physiopathology:
  - Direct toxicity of MMA on the tube
  - Mitochondrial dysfunction > apoptosis
Indication of transplantation

- **Objectives:**
  - To improve the metabolic disorders (less decompensation)
  - Increase protein intake, better nutrition
  - Quality of life

- **Transplantation:**
  - Ubiquititary enzyme, liver +++ kidney + (18%)
  - Liver alone: decrease MMA but does not avoid renal insufficiency
  - Kidney alone: increase MMA excretion and bring the enzyme
Questions

• Which patient to be transplanted?
• When?
• K / L / L + K?

• Our experience in Necker:
  – 5 K alone
  – 3 K + L
  – No L alone
MMA : kidney transplantation alone
Necker Experience

Renal transplantation in 4 patients with methylmalonic aciduria: A cell therapy for metabolic disease

A. Brassier a, O. Boyer b, V. Valayannopoulos a, C. Ottolenghi c, P. Krug b, M.A. Cosson a, G. Touati a, J.B. Arnoux a, V. Barbier a, N. Bahi-Buisson d, I. Desguerre d, M. Charbit b, J.F. Benoist e, L. Dupic f, Y. Aigrain g, T. Blanc g, R. Salomon b, D. Rabier c, G. Guest b, P. de Lonlay a, P. Niaudet b,*

Mol Genet and Metabol 2013

- Improvement of the metabolic disease (sMMA and uMMA)

But

- Modest augmentation of the protein intake (0,6 > 0,66 g/kg/j)

- Modest neurologic improvement but less decompensations
## Table I. Demographic, diagnostic, and surgical data of patients (n = 14) who received LKT or LT at Lucile Packard Children’s Hospital at Stanford between December 1997 and May 2012

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Time of diagnosis</th>
<th>Identified by NBS</th>
<th>Diagnosis*</th>
<th>Age at Tx</th>
<th>Procedure</th>
<th>Graft</th>
<th>Long-term immunosuppression</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>Neonatal</td>
<td>no</td>
<td>Non-B12-responsive clinically</td>
<td>10 y 9 mo</td>
<td>LKT</td>
<td>Whole</td>
<td>Prednisone, tacrolimus</td>
<td></td>
</tr>
</tbody>
</table>
| 2       | M   | Neonatal         | no               | fibroblast assay, mut^c        | 20 y 8 mo  | LKT, bilateral nephrectomy | Whole | Prednisone, tacrolimus, sirolimus | 1. Re-exploration, bleeding  
          |      |                  |                  |            |           |           |       |                             | 2. Post-transplant diabetes mellitus and hypertension attributed to immunosuppressive regimen |
| 3       | M   | Neonatal         | no               | Fibroblast assay, mut^c        | 5 y 11 mo  | LKT, bilateral nephrectomy, splenectomy | Whole | Prednisone, tacrolimus, sirolimus | 1. Spontaneous splenic rupture → splenectomy  
          |      |                  |                  |            |           |           |       |                             | 2. Re-exploration, bleeding  
          |      |                  |                  |            |           |           |       |                             | 3. Seizure POD12 (high tacrolimus level) |
| 4       | M   | Neonatal         |                  |                          | 11 y 2 mo  | LKT, right nephrectomy, splenectomy | Whole | Sirolimus |               |
| 5       | F   | Neonatal         | yes              | c.682C>T (p.R228X), c.1106 G>A (p.R369H) | 3 y 3 mo  | LT        | Whole | Tacrolimus, mycophenolate | Mild acute rejection 4 weeks post-transplantation, received steroids |
| 6^l     | F   | 3 mo             | no               | c.322C>T (p.R108C)           | 15 y 4 mo  | LKT       | Whole | Prednisone, tacrolimus, mycophenolate |               |
| 7       | F   | Neonatal         | yes              | c.682C>T (p.R228X), c.581C>T (p.P194L) | 11 mo      | LT        | Whole | Tacrolimus |               |
| 8       | F   | 9 mo             | no               | c.572C>A (p.A191E)           | 17 y 6 mo  | LKT, splenectomy | Whole | Tacrolimus, mycophenolate | Re-exploration, drainage of subphrenic abscess  
          |      |                  |            |            |           |           |       | Tacrolimus, mycophenolate | Acute rejection 3 weeks post-transplant |
| 9       | M   | Neonatal         | no               | c.349G>T (p.E117X), c.1038_1040 delTCT | 8 y 10 mo  | LKT       | Whole | Prednisone, tacrolimus, mycophenolate |               |
| 10      | M   | 2 y              | no               | Fibroblast assay, mut^c       | 16 y 1 mo  | LKT       | Whole | Tacrolimus |               |
| 11      | F   | Neonatal         | yes              | c.682C>T (p.R228X)           | 10 mo      | LT        | Whole |               | 1. 1st transplantation: Hepatic artery thrombosis POD5 → re-transplantation.  
          |      |                  |              |            |           |           |       |                | 2nd transplantation: No complications |
| 12      | F   | Neonatal         | yes              | c.1399C>T (p.R467X)          | 1 y 1 mo   | LT        | Whole | Seg 2-4 | Tacrolimus | Mild acute rejection POD10, received dose of steroids |
| 13^j    | F   | Neonatal         | yes              | c.1399C>T (p.R467X) c.682C>T (c.R228X) p.A732WFX3 | 1 y 2 mo   | LT        | Seg 2-4 | Tacrolimus |               |
| 14      | F   | Neonatal         | yes              | c.682C>T (c.R228X) p.A732WFX3 | 1 y 8 mo   | LT        | Whole | Tacrolimus |               |
DFG
Serum MMA

30 - 40 ml/min/1.73m²

L + K transplantation

KDIGO
Transplantation in MMA

- Serum creatine is not a good marker of GFR (reduce muscle mass)
- Decline GFR can occur before the age of 10
- Dialysis does not eliminate MMA efficiently (PD or HD or both ?)
- KT alone might limit the occurrence of metabolic decompensations
- LKT when GFR around 30 – 40 ml/min/1.73m2
- LT alone before GFR decline is a good option (Standford’s experience)
- What is the GFR decline after LT alone?
- Which option when GFR 40 – 80?
DFG

Serum MMA

30 - 40

L transplantation

L + K transplantation

ml/min/1.73m²

KDIGO
Q7. What is the optimal timing for transplant and role/utility of pre-emptive transplantation? How can we better address the risk of disease recurrence post-transplant?

High risk of recurrence:
- Rapid occurrence of ESRD
- Recurrence on first graft
- Initial steroid-sensitivity
- (Molecular signature)

Recurrence in nephrotic syndrome

1. Iv CsA
2. Rituximab
3. Abatacept
   - Galactose
   - Anti-TNFα

High dose of steroids
Transplantation in hyperoxaluria

ml/min/1.73m²

DFG

Transplantation

KDIGO

30 - 40

oxalemia
Transplantation in hyperoxaluria

Transplantation (per-op HD)

Ox accumulation in tissues

Prolonged hyperhydration + alcalinisation after transplantation

DFG

ml/min/1.73m²

30 - 40

oxalemia

KDIGO
Transplantation in hyperoxaluria

- Oxalemia
- Dialysis (HD +/- PD)
- Prolonged hyperhydration + alcalinisation after transplantation

KDIGO
Q9. How can growth-related issues and treatment be optimally managed?

Long-term growth hormone treatment in short children with CKD does not accelerate decline of renal function: results from the KIGS registry and ESCAPE trial

Otto Mehl1, Anders Lindberg2, Dieter Haffner3, Franz Schaefer1, Elke Wühl1. for members of the German KIGS Board · ESCAPE Trial Group

Changes in estimated glomerular filtration rate (eGFR) from the start of treatment is shown as growth hormone; eGFR, estimated glomerular filtration rate; ns, not significant.
Q9. How can growth-related issues and treatment be optimally managed?

Considerable variations in growth hormone policy and prescription in paediatric end-stage renal disease across European countries—a report from the ESPN/ERA-EDTA registry

M. van Huis¹, M. Bonthuis², E. Sahpazova³, F. Mencarelli⁴, B. Spasojević⁵, G. Reusz⁶, A. Caldas-Afonso⁷, A. Bjerre⁸, S. Baiko⁹, K. Vondrak¹⁰, E.A. Molchanova¹¹, G. Kolvek¹², N. Zaikova¹³, M. Böhm¹⁴, G. Ariceta¹⁵, K.J. Jager², F. Schaefer¹⁶, K.J. van Stralen² and J.W. Groothoff¹
In 21 out 28 countries GH is reimbursed
In 15, there is a national policy (and they are quite different)

Table 3. Actual use of rGH and patients with short stature on dialysis

<table>
<thead>
<tr>
<th>Country</th>
<th>% of rGH use</th>
<th>Eligibility according to short stature (height SDS less than −2)</th>
<th>Eligibility according to national criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>% of patients eligible for rGH</td>
<td>% of eligible patients receiving rGH</td>
</tr>
<tr>
<td>Belgium</td>
<td>40.2</td>
<td>33.5</td>
<td>49.7</td>
</tr>
<tr>
<td>Czech Republic</td>
<td>22.2</td>
<td>42.0</td>
<td>16.7</td>
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<tr>
<td>Estonia</td>
<td>50.0</td>
<td>83.3</td>
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<tr>
<td>Greece</td>
<td>18.8</td>
<td></td>
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<tr>
<td>Italy</td>
<td>20.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lithuania</td>
<td>6.8</td>
<td></td>
<td></td>
</tr>
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<td>The Netherlands</td>
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<td>Portugal</td>
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<tr>
<td>FYR of Macedonia</td>
<td>33.3</td>
<td>44.4</td>
<td>50.0</td>
</tr>
<tr>
<td>Serbia</td>
<td>34.9</td>
<td>54.3</td>
<td>42.4</td>
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<td>Spain</td>
<td>24.8</td>
<td>39.2</td>
<td>33.6</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>11.6</td>
<td>53.8</td>
<td>15.9</td>
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<tr>
<td>Overall</td>
<td>21.7</td>
<td>45.9</td>
<td>26.0</td>
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</table>

Table 4. Actual use of rGH and patients with short stature on transplantation

<table>
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<tr>
<th>Country</th>
<th>% of rGH use</th>
<th>Eligibility according to short stature (height SDS less than −2)</th>
<th>Eligibility according to national criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>% of patients eligible for rGH</td>
<td>% of eligible patients receiving rGH</td>
</tr>
<tr>
<td>Belgium</td>
<td>19.9</td>
<td>51.9</td>
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<td>13.7</td>
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<tr>
<td>United Kingdom</td>
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<td>45.4</td>
<td>6.6</td>
</tr>
<tr>
<td>Overall</td>
<td>5.5</td>
<td>38.9</td>
<td>8.9</td>
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</tbody>
</table>
Thank you for your attention

remi.salomon@aphp.fr