Renal involvement in inborn errors of metabolism

[No conflict of interest]

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Introduction

- Around 80 IEM with potential renal involvement...

- Classification into 13 groups...
Eimie - girl, 2.7 yrs

- Severe scoliosis in both parents
- Birth: 38 GA term, 3300 g, 50 cm, HC 34 cm
- Vitamine D: daily from birth to 1.5 yrs, then 1 load dose per year
- Immunization: ok
- Progressive deformation of both legs at the time of walking learning

- Plain x-ray at 2.5 yrs

Rickets
Eimie - girl, 2.7 yrs

- Clinical examination
  - Height 92.cm (+0,5 SD) – BW 13,2 kg (N)
  - BP 88/60
  - Intercondylar distance 6 cm
  - Liver enlargement 4 cm

- Abdomen US
  - Hepatomegaly
    - Heterogenous parenchyma
    - Small hypo- and hyperechogenic nodules
    - Normal gallbladder
  - Mild renal enlargement
  - No abdominal mass
  - No lymph node
Eimie - girl, 2.7 yrs

- Biological investigations
  - Calcium 2.35 mmol/L
  - Phosphate 0.57 mmol/L (N= 1.39-2.20)
  - Bicarbonate 16 mmol/L
  - Chloride 119 mmol/L
  - Creatinine 17 mmol/L
  - Alk. Phosph. 1251 IU/L (N<500)
  - Platelet count 94 G/L
  - ASAT 61 IU/L (N= 5-34)
  - GGT 79 IU/L (N= 5-25)

- Diagnosis?
- Specific tests?
Eimie - girl, 2.7 yrs

- **Diagnosis:** Tyrosinemia type 1
- **Specific tests**
  - Alpha-fetoprotein 2345 µg/L (N< 9)
  - Urine succinyl-acetone 179 µmol/L (N< 1)
- **After 2.5 mos on NTBC**
  - 415
  - < 1
- **Comments**
  - Incidence: 1/200,000 (Canada) to 1/2,000,000 live births (Europe)
  - Autosomal recessive inheritance
  - Most common presentation: acute liver failure in the 1st year of life
  - Fumaryl-acetoacetase deficiency (enzyme for tyrosine degradation) - *FAH*, 15q23-q25
  - Increased plasma delta aminolevulinic acid + urine succinyl-acetone
    - Liver toxicity: cirrhosis, hépatocarcinoma
    - Kidney: Fanconi syndrome
  - From 1990: NTBC (Orfandin®) – blocks tyrosine degradation – hyper-tyrosinemia
    - Risk of painful dermatological and ocular lesions
    - Limitation of tyrosine intake (low protein diet + specific aminoacids supplements)
  - Some patients may require liver Tx
1. IEM of amino acids and peptides

- Cystinosis
- **Tyrosinemia type 1**
- Lysinuric protein intolerance
- Cystinuria
- Propionic acidemia
- Methylmalonic acidemia
- Prolidase deficiency
- Alkaptonuria
- Homocystinuria
- Oxoprolinuria

- Fanconi - CKD
- Fanconi - CKD
- TIN - CKD
- Stones
- CKD
- TIN - CKD
- Lupus nephritis
- Black urine
- Renal infaction
- Stones
1. IEM of aminoacids and peptides

- Cystinosis
- Tyrosinemia type 1
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- **MethyImalonic acidemia**
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<table>
<thead>
<tr>
<th>Disease</th>
<th>Condition</th>
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<tbody>
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<td>Fanconi - CKD</td>
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Methylmalonic acidemia (MMA)

- Severe inborn error of catabolic pathway of branched-chain aminoacids, odd chain fatty acids and cholesterol leading to accumulation of MMA in the serum
- Caused by mutations
  - In the MUT gene encoding methylmalonylCoA mutase (isolated MMA)
  - in the MMAA (CblA) and MMAB (CblB) genes encoding key enzymes of the metabolism of its cofactor, cobalamin (vitamin B12)
- These enzymes are expressed in many tissues, including liver and kidney
- Methylmalonyl CoA mutase can be completely deficient (mut°) or partially deficient with residual activity (mut−)

Clinical presentation
- Lethargy, vomiting, dehydration, metabolic acidosis and coma in the neonatal period
- Or later in case of partial deficiency
MMA - Management

- (Vitamin B12 in responsive patients)

- In nonresponsive patients: low-protein high-energy diet
  - Supplementary amino-acids avoiding the propiogenic ones (valine, isoleucine, threonine and methionine)
  - L-carnitine to prevent deficiency and increase the excretion of carnitine esters

- Antibiotics intermittently to reduce propionate production by gut flora
MMA – Renal involvement

- Proximal and/or distal tubular dysfunction
- Progressive tubulointerstitial disease
- Leading to ESRD in >50% of those with severe forms of MMA
- CKD can be present as early as 18 mo
- Decreased muscle mass renders creatinine assessment poorly predictive
MMA – Transplantation strategy

Renal transplantation in 4 patients with methylmalonic aciduria: A cell therapy for metabolic disease
Molecular Genet Metab 2013

Improvement in the prognosis and development of patients with methylmalonic acidemia after living donor liver transplant
Rieko Sakamoto, Kimitoshi Nakamura, Jun Kido, Shiro Matsumoto, Hiroshi Mitsubuchi, Yukihiro Inomata, Fumio Endo
Transplantation 2016
2. IEM of fatty acids and ketone bodies

- CPT deficiency 1: RTA
- CPT deficiency 2: Renal cysts – CKD
- Fatty acid oxidation disorders: Tubulopathy - AKI
3. IEM of carbohydrates

- Galactosemia
  - Fanconi
- Glycogen storage disease type 1a
  - Fanconi – Stones – FSGS
- Glycogen storage disease type 1b
  - FSGS
- Fanconi-Bickel syndrome
  - Fanconi – Hyperfiltration
- Hereditary fructose intolerance
  - Fanconi – AKI
- Congenital lactase deficiency
  - Nephrocalcinosis
- Glucose-galactose malabsorption
  - Stones
- Transaldolase deficiency
  - Tubulopathy – Stones
- Primary hyperoxalurias 1, 2, 3
  - Stones – CKD – Systemic inv.
- Renal glycosuria
  - Glycosuria
- McArdle disease
  - AKI - Myoglobinuria
3. IEM of carbohydrates

- Galactosemia
- **Glycogen storage disease type 1a**
- Glycogen storage disease type 1b
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  - Fanconi
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  - Stones
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  - Glycosuria
  - AKI - Myoglobinuria
Glycogen Storage Disease Type 1

- Autosomal recessive inheritance
- Defects in the G6Pase complex (conversion from G6P into glucose)
  - Accumulation of glycogen in the liver, kidney and intestine mucosa
- Poor tolerance to fasting: hypoglycemia, lactic acidosis, hyperuricemia
- Growth retardation, hepatomegaly (risk of hepatocarcinoma)
- Improved prognosis due to better dietary/metabolic management (frequent feed + uncooked cornstarch)
- Renal dysfunction in the long term: PU, HTN, CKD
- Pathophysicsology: diabetes mellitus + specific GSD-1 involvement
GSD-1: Renal involvement

**Renal tubular dysfunction**
- Proximal tubular dysfunction: early feature (PU, enzymuria)
- Fanconi syndrome is rare
- Distal tubular dysfunction
- Higher risk of nephrolithiasis (hypercalciuria + hypocitraturia)

**Glomerular dysfunction**
- Hyperfiltration + albuminuria in most patients > 25 yrs of age
- Progressive FSGS with decline in GFR
- Treatment with ACEi/ARB slows down the progression of CKD
- Some patients may require combined liver-kidney Tx
4. IEM of energy (mitochondrial cytopathies)

- GRACILE syndrome
- Pyruvate carboxylase deficiency
- Kearns Sayre syndrome
- MELAS
- MIDD
- NN encephalopathy-cardiomyopathy
- Coenzyme Q10 deficiencies
- Mitochondrial ribonucleotide sub. 2
- Pearson syndrome
- Complex III deficiency
- Complex IV deficiency
- mtDNA depletion

Cf. Francesco Emma’s presentation!
5. IEM of purines, pyrimidines and nucleotides

- SCID-ADA deficiency: RTA, proteinuria
- Lesch-Nyhan syndrome: Stones, AKI, CKD
- Familial hyperuricemic nephropathy: Gout, stones, CKD
- APRT deficiency: Stones 2,8-dihydroxyadenine
- Hereditary renal hypouricemia: Stones, AKI
- Hereditary orotic aciduria: Stones
- Xanthinuria type 1: Stones
- Xanthinuria type 2: AKI
- PRPP synthetase superactivity: Stones
5. IEM of purines, pyrimidines and nucleotides

- SCID-ADA deficiency: RTA, proteinuria
- **Lesch-Nyhan syndrome**: Stones, AKI, CKD
- Familial hyperuricemic nephropathy: Gout, stones, CKD
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- PRPP synthetase superactivity: Stones
Lesch-Nyhan syndrome

- Deficiency of hypoxanthine-guanine phosphoribosyltransferase (HPRT)
- Lesh-Nyhan syndrome is the most severe form
- Prevalence: 1/380,000 (Canada) – 1/235,000 (Spain)
- X-linked recessive – Xq26 - > 300 diseases associated-mutations in HPRT1
- Uric acid overproduction – Nephrolithiasis and gout
- Progressive neurological involvement related to enzyme deficiency
- Neurological manifestations
  - Severe action dystonia
  - Choreoathetosis and ballismus
  - Cognitive and attention deficit
  - Self-injurious behaviour, sensitive to any kind of stimuli (pain, anxiousness, etc.)
Lesch-Nyhan syndrome

- Diagnosis: HPRT activity in erythrocytes + genotyping (prenatal diagnosis)

- Management
  - Allopurinol, adapted to avoid xanthine stones
  - Spasticity: benzodiazepins, baclofen
  - Physical rehabilitation: limited efficacy
  - Stereotaxic neurosurgery: limited efficacy
  - Psychological care of the child and parents
  - Self-injurious behaviour: physical restraints, behavioural and physical actions
Lesh-Nyhan syndrome: Self-injurious behavior

With permission

Torres Orphanet J Rare Dis 2007
6. IEM of Sterols

- Smith-Lemli-Opitz syndrome: Renal cysts, CAKUT
- Conradi Hunnerman syndrome: Renal hypo/dysplasia
- CHILD syndrome: Renal hypo/dysplasia
- Desmosterolosis: Renal hypo/dysplasia
- Antley-Bixler syndrome: Renal hypo/dysplasia
7. IEM of lipid and lipoprotein metabolism

- Lecithin: cholesterol acetyltransferase deficiency  PU, GN, CKD

- Lipoprotein glomerulopathy  PU, GN, CKD
8. IEM of Glycosylation

- **Type 1a**: Proteinuria – NS – cysts
- **Type 1h**: Renal cysts – Tubulopathy
- **Type 1l**: Renal cysts
- **B3GALTL (Peter-plus syndrome)**: CAKUT
- **Type 2f**: Proteinuria
- **Type 2e**: CAKUT - Tubulopathy
9. Lysosomal disorders

- Fabry’s disease: RTA – proteinuria – CKD
- Metachromatic leucodystrophy: RTA – Tubulopathy
- Galactosialidose: Proteinuria – CKD
- MPS type 1 (Hurler): NS – Hypertension
- Infantile sialic acid storage disease: Proteinuria – NS
- Gaucher’s disease: Proteinuria – Acute GN
- Action myoclonus renal failure Sd: Proteinuria - FSGS
9. Lysosomal disorders

- **Fabry’s disease**
  - RTA – proteinuria – CKD

- Metachromatic leucodystrophy
  - RTA – Tubulopathy

- Galactosialidose
  - Proteinuria – CKD

- MPS type 1 (Hurler)
  - NS – Hypertension

- Infantile sialic acid storage disease
  - Proteinuria – NS

- Gaucher’s disease
  - Proteinuria – Acute GN

- Action myoclonus renal failure Sd
  - Proteinuria - FSGS
Fabry’s disease

- X-linked inherited lysosomal storage disorder
- Deficiency of $\alpha$-galactosidase A
- Progressive accumulation of globotriaosylceramide (Gb3)
- Signs and symptoms can begin in early childhood and lead to life-threatening renal, cardiac and cerebrovascular disease
- Early diagnosis is important to prevent irreversible pathology
- Diagnosis based on $\alpha$-Gal A enzyme activity and/or genotyping
A systemic disease

Accumulation in many types of cells

- CNS
- Skin
- Heart
- Kidney
- Vascular endothelium

Early symptoms:
- Pain
- GI
- Skin

Late symptoms:
- Kidney
- Heart
- Brain
Characteristic pictures in adults

Angiokeratomas

Cornea verticillata
≈15 year-delay from first symptoms to diagnosis

Mainly due to:
- Nonspecific nature of early symptoms
- Heterogeneous phenotypes
- Lack of disease awareness among physicians
Specific signs to pediatric patients

- Acro-syndrome
  - Acroparesthesia, pain attacks (extremities) ± fever
  - Raynaud’s phenomenon

- Skin lesions (ear telangiectasias, small angiokeratomas)

- Hypo/anhidrosis, poor tolerance to cold and heat

- Eye abnormalities (conjunctival telangiectasias, corneal whorls)
Laboratory diagnostic confirmation

**Males**
Males typically have <1% of normal enzyme activity in plasma and leukocytes

- **α-GAL enzyme assay**
  - Plasma, leukocytes, cultured skin fibroblasts, dried blood
  - Low activity

- **DNA analysis**
  - Fabry GLA gene mutation

**Females**
Females may have normal to low-normal enzyme activity

- **DNA analysis**
  - Fabry GLA gene mutation

**Fabry disease diagnosis confirmed**
Global Fabry nephropathy spectrum

- GL-3 accumulation in renal cells
- End-stage renal disease in 3rd-5th decade of life
- Premature death
- Fabry nephropathy
- Proteinuria
- Progressive GFR decline
- Hypertension

Burden of Renal Disease

- Infant
- Child
- Adolescent
- Adult

Progressive renal insufficiency
Irreversible glomerular changes, tubular atrophy
GL-3 accumulation in renal cells
Typical GL-3 inclusion bodies

Electron microscopy

Courtesy of Dr M Gubler, Necker Hospital Paris
Early progressive damage to podocytes

- Decreased endothelial cell fenestrations
- Glomerular basement membrane loss of integrity of slit diaphragms
- Widened podocyte foot processes
- Decreased endothelial cell fenestrations

_Courtesy of Dr M Mauer, University of Minnesota_
Progressive loss of GFR leading to RRT

Fabry Registry patients (ERT naive) starting RRT:

- 14% males - 2% females
- Median age: 38 years for both genders
- Youngest patients starting RRT: age 15 in male – 17 in female
- ESRD occurred most often in the 3rd to 5th decades of life
Management

- Optimal care involves disease-specific and supportive treatment
- Available therapies include:
  - Enzyme replacement therapy (ERT) - agalsidase: Addresses the underlying pathophysiology by replacing deficient α-Gal A
  - Adjunct therapies, e.g.
    - Pain management (anti-psychotics, anti-epileptics, opiates, NSAIDs, etc.)
    - ACEI/ARBs +++
    - Renal replacement therapy
    - Anti-depressants
    - Hearing aids
    - Cardiac pacing

Results of ERT on renal tissue

1-year follow-up of ERT in an 18 year-old male

Baseline

12 mos on ERT

GL-3 exocytosis from podocytes

Najafian *PLoS ONE* 2016
5-6 year follow-up of ERT in pediatric patients

Urine albumin/creatinine ratio

mGFR

Plasma GL-3

Urine GL-3

Tøndel 2013
Patients who initiated treatment at a younger age and with less kidney involvement benefited the most from therapy. Patients who initiated treatment at older ages and/or had advanced renal disease experienced disease progression.
In conclusion, among patients with mutant α-galactosidase forms that were suitable or not suitable for migalastat therapy, the percentage of patients who had a decrease of 50% or more in the number of GL-3 inclusions per kidney interstitial capillary at 6 months did not differ significantly between the migalastat group and the placebo group.
10. Peroxisomal disorders

- Zellweger syndromes
- Renal cysts

11. IEM of vitamins and (non-protein) cofactors

- Imerslund-Grasbeck syndrome
  - LMW proteinuria
- Cobalamin deficiencies cblC, cblD, etc.
  - HUS – Glomerulopathy
- MTHDH deficiency
  - HUS
- Hypophosphatasia
  - Nephrocalcinosis
### 12. IEM of trace elements and metals

<table>
<thead>
<tr>
<th>Disease/Deficiency</th>
<th>Clinical Manifestations</th>
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<tbody>
<tr>
<td>Wilson’s disease</td>
<td>Fanconi – Proteinuria</td>
</tr>
<tr>
<td>Menke’s disease</td>
<td>Stones – CKD</td>
</tr>
<tr>
<td>Molibdenum cofactor deficiency</td>
<td>Xanthine stones</td>
</tr>
<tr>
<td>Carbonic anhydrase II deficiency</td>
<td>Mixed type of RTA</td>
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### 13. IEM of porphyrin and heme

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<tr>
<th>Disease/Deficiency</th>
<th>Clinical Manifestations</th>
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<tbody>
<tr>
<td>Doss hepatic porphyria</td>
<td>Urine turn red-purple</td>
</tr>
<tr>
<td>Acute intermittent porphyria</td>
<td>Urine turn red-purple – CKD</td>
</tr>
<tr>
<td>Hereditary coproporphyria</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Porphyria variegata</td>
<td>Hypertension</td>
</tr>
</tbody>
</table>
Conclusions

- A group of rare/heterogenous diseases
- Renal involvement is common in IEM, ranging from first-line presentation (e.g., cystinosis, APRT deficiency, etc.) to minor sign in a patient with major extrarenal involvement (e.g., metachromatic leucodystrophy, Lesch-Nyhan syndrome, etc.)
- IEM should be suspected in case of unexplained
  - Fanconi syndrome
  - Nephrocalcinosis, nephrolithiasis (stone analysis ++)
  - Proteinuria ± nephrotic syndrome (kidney biopsy ++)
  - Atypical cystic disease
- Mainly if associated with extrarenal abnormalities
- The management relies on treating the primary defect
- The prognosis often depends on extrarenal involvement
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