Kongenitala nefroser och genetik

Christer Holmberg
Hospital for Children and Adolescents
University of Helsinki
Helsinki, FINLAND
Clinical classification of nephrotic syndrome (NS)

- **Onset of symptoms**
  - Congenital NS (0-3 months)
  - Infantile NS (4-12 months)
  - Childhood NS (> 12 months)
  - Congenital + infantile = early onset NS

- **Response to therapy**
  - Steroid sensitive NS
  - Steroid resistant NS
1950----------2017
## CNS - history

### Hallman, Hjelt, Ahvenainen, 1956

- 8 patients
- Clinical picture defined

### Table I. CNSY Cases Reported in Literature

<table>
<thead>
<tr>
<th>Year</th>
<th>Authors</th>
<th>Number of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>1942</td>
<td>Gautier and Miville</td>
<td>1</td>
</tr>
<tr>
<td>1950</td>
<td>Lyttle and Goettsch</td>
<td>1</td>
</tr>
<tr>
<td>1951</td>
<td>Fanconi et al.</td>
<td>3 (siblings)</td>
</tr>
<tr>
<td>1954</td>
<td>Kunstadter et al.</td>
<td>1</td>
</tr>
<tr>
<td>1954</td>
<td>Eiben et al.</td>
<td>1</td>
</tr>
<tr>
<td>1954</td>
<td>Frischknecht et al.</td>
<td>1</td>
</tr>
<tr>
<td>1957</td>
<td>Giles et al.</td>
<td>3 (2 siblings)</td>
</tr>
<tr>
<td>1957</td>
<td>Hudson (cited by Giles)</td>
<td>2 (siblings)</td>
</tr>
<tr>
<td>1957</td>
<td>Dobbs and France</td>
<td>1</td>
</tr>
<tr>
<td>1957</td>
<td>(cited by Giles)</td>
<td></td>
</tr>
<tr>
<td>1957</td>
<td>Vernier et al.</td>
<td>1</td>
</tr>
<tr>
<td>1957</td>
<td>Gruskay and Turane</td>
<td>3 (siblings)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td><strong>18</strong></td>
</tr>
</tbody>
</table>
CNS - etiology?

- infection, nephrotoxic, immunological lesion??

- genetic??
  - several siblings
  - Giles et al. 1957 (intermarriage)
  - Hereditary!!

Norio, 1966
- 57 evident CNS families

- Autosomal recessive inheritance
THE LOW-WEIGHT GROUPS AND HAEMODIALYSIS

TOM AHOLA, HELINA BJÖRKMAN, PAAVO MAKELÄ, MIKKO PASILA, JUSSI VILSKA and NIilo HALLMAN

From the Children's Hospital, University of Helsinki, Helsinki, Finland

Table 2. The treated infants

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (mo.)</th>
<th>Weight (kg)</th>
<th>Surface area (m$^2$)</th>
<th>Diagnosis</th>
<th>Indication</th>
<th>No. of dialysis</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>R. A.</td>
<td>17</td>
<td>12.6</td>
<td>0.52</td>
<td>Tubular necrosis</td>
<td>Anuria</td>
<td>2</td>
<td>Recovery</td>
</tr>
<tr>
<td>L. J.</td>
<td>24</td>
<td>11.5</td>
<td>0.50</td>
<td>Stenosis Inf. et valv. a. pulm.</td>
<td>Anuria post operat.</td>
<td>1</td>
<td>Recovery</td>
</tr>
<tr>
<td>A.-M. P.</td>
<td>13</td>
<td>9.8</td>
<td>0.44</td>
<td>Hemol. urmic syndrome</td>
<td>Anuria</td>
<td>5</td>
<td>Recovery</td>
</tr>
<tr>
<td>H. P.</td>
<td>18</td>
<td>11.4</td>
<td>0.49</td>
<td>Hemol. urmic syndrome</td>
<td>Anuria</td>
<td>2</td>
<td>After 3 months residual haematuria + proteinuria</td>
</tr>
<tr>
<td>T. K.</td>
<td>2</td>
<td>4.0</td>
<td>0.23</td>
<td>Cong. nephrosis</td>
<td>Bilateral nephrectomy</td>
<td>6</td>
<td>Died of septic infection</td>
</tr>
<tr>
<td>J. G.</td>
<td>23</td>
<td>6.8</td>
<td>0.32</td>
<td>Cong. nephrosis</td>
<td>Bilateral nephrectomy</td>
<td>9</td>
<td>Died after a transplantation attempt</td>
</tr>
<tr>
<td>P. T.</td>
<td>4.5*</td>
<td>3.2*</td>
<td>0.21*</td>
<td>Cong. nephrosis</td>
<td>Bilateral nephrectomy</td>
<td>50+</td>
<td>Under regular dialysis</td>
</tr>
</tbody>
</table>

* Values at bilateral nephrectomy.
CNS - Renal Transplantation

- Hoyer, Lancet 1973
- Mahan et al., 1984
  - 41 pts 24 treated after 1971
  - steroids, cytotoxics....no effect
  - agressive nutrition, 8 bilateral nephrectomy
  - 44% family history, 22% Finnish anc.
  - 2 year PS 80%, GS 71%
  - height -3.1 SD, 80 % normal school
Renal transplantations in children

- Helsinki
  - 1986 renal  298
  - 1987 liver  141
  - combined  12
  - 1991 heart  84
  - 2007 lung  4
  - 2009 intestine  4

- 107 CNF patients transplanted
CNS - Renal transplantation

Jahnukainen et al. 2016
Hölttä et al., 2016
Natural history without therapy

- Reduced growth and development
- Infections
- Thrombotic events
- Sudden death
- Renal failure
- (Wilms tumor/s)
CNS – Renal Transplantation

**Treatment:**
- nutrition
- albumin
- anticoagulation
- thyroxin
- treatment of infections
- vitamins

**Dialysis:**

**Nephrectomy?**
Parenteral protein supplementation

- Depends on the protein losses

- Intravenous albumin infusions
  - 20% albumin infusions + furesis 0.5 mg/kg
  - Infusions started x3-4/day,
  - One infusion (6-8 h) at night
  - Albumin amount 1-4 gr/kg/d
    - Oedem, blood pressure, weight gain
    - P-albumin, >15 g/l

- Central vein catheter
  - At the age of 2-3 weeks in CNF
Medical management

Hypothyroidism
- Heavy proteinuria leads to losses of TBG, T4, T3
- Clinical significance somewhat open
- Thyroxin substitution 6.25-50 ug/d
- TSH follow-up

Thrombotic events
- Anti-coagulants (AT III) lost into urine
- Warfarin therapy
  - In CNF started at the age of 2-3 weeks
- AT III (50 u/kg)
  - before surgical procedures
Nutrition

Optimal nutrition

- Breast milk/normal formula 100–130 ml/kg/day
- 100–130 kcal/kg/day
- proteins 4 g/kg/day
- lipid supplementation (rapeseed/sunflower oil)
- A, D, E and water soluble vitamins
- calcium, magnesium (potassium) supplementation

- Nasogastric tube or gastrostomy often required
ACE inhibitor and indomethacin therapy

Primary therapy:
- ACE-inhibitor (captopril 1-5 mg/kg/d)

If pure response:
  - ATII blocker added (losartan 0.3-1.4 mg/kg/d)

If pure response:
  - Indomethacin added (1-5 mg/kg/d)

Renal function!

Patients with severe genetic mutations (truncated protein, no expression) hardly response
Therapy if severe proteinuria

- Nephrectomy – dialysis – renal transplantation

  - to reduce protein loss and correct its consequences; corrects protein deficiency, improves growth, corrects coagulation defect, hypothyreosis and risk for severe infections

  - to improve quality of life for the child and its family, can be at home

  - unilateral nephrectomy??

  - BUT: terminal renal failure, dialysis and medication
CNS - nephrectomy

Unilateral
Coulthard et al., 1989

Bilateral
Holmberg et al., 1995

- When severe protein loss
- No reaction to medication
- Reduced growth and QOL for patient and family
- Complications
- Experienced centre
Nephrectomy

- No nephrectomy needed
  - Development of renal failure and fibrosis reduces proteinuria

- Unilateral nephrectomy
  - To reduce protein losses
  - Improvement of quality of life
  - Used in some centers with good results

- Bilateral nephrectomy + dialysis
  - To stop massive proteinuria + complications

- In Denys-Drash
  - To prevent (treat) Wilm’s tumor
Growth in a Finnish NPHS1 patient diagnosed at birth
Growth in a Finnish NPHS1 patient diagnosed at 5 months of age
Growth and puberty after renal transplantation

Growth of 23 CNS children on PD

- 109 children transplanted at a mean age of 4.5 years:

- normal puberty

- final height
  boys 169 cm ( -1.2 SD )
  girls 154 cm ( -1.7 SD )
Neuromotor development in 23 CNS children with and without comorbidity
CRF in infancy; neurological outcome

- Valanne et al. 2004
  - 33 pts/29 NPHS1 Tx>5y
  - 54% ischemic lesions in vascular border zones/haemodynamic crises
  - 15% reversible atrophy

- Qvist et al. 2002
  - 79% normal school
  - 76% normal motor perf.

- Laakkonen et al. 2011
  - 21 pts/15 NPHS1 CCPD at 0.59y
  - 52% comorbidity or risk factor for abnormal dev.
  - 30% normal, 43% minor imp. and 29% major imp. (all comorb. or risk factor)
Neurodevelopmental outcome of 21 CNS children

- 29% normal
- 43% minor impairment
- 29% major impairment

All attended full time school
Early CNS patients had neurological problems (no anticoagulation!) and 54% arterial border zone infarcts.

21 pts treated 1987-1995, > 50% CNS assessed for HRQL at 6 y and adults (21 y) and CBCL and ASR:
- 52% secondary level or vocational education (N=66%)
- ASR normal range
- HRQL 0.94/controls 0.97, = as in all chronically sick pts.
- some visuomotor and verbal impairment = test and support!!
- those with early arterial border zone infarcts did as well as the others!!
Neoropsychological development; comorbidity and CNF
Haavisto et al., 2012, 2013

[Bar charts showing IQ scores for Full-Scale, Verbal, and Performance IQ, comparing All patients, Patients without neurological comorbidity, and Patients with neurological comorbidity. Another set of bar charts compares Non-CNF (n=18) and CNF (n=21) groups.]
Infants in PD; family coping
Laakkonen et al., 2014

Spousal relationship quality

Parental expressed emotions

Time point

Percent

Time point

Percent
Kidney transplantation

- Results in infants as good as in older children
  - US: DD allograft survival 93 % at 3 years
  - LD allograft survival 95 % at 3 years
  - Scandinavia: All survivals in infants equal to older children

- Extraperitoneal placement possible when recipient weight 9-10 kg
  - 1.5 x fluids during the early weeks

- Genetic diseases do not show recurrence
  - An exception is a CNF child with two severe truncating mutations (Fin-major homozygotes)
What is wrong in CNF??

Glomerular filter

Podocyte foot process

Slit diaphragm

Basement membrane

Endothelium
Gene for Congenital Nephrotic Syndrome

Kestilä et al. Cell, 1; 575-582, 1998
Nephrin is located at the slit diaphragm

Ruotsalainen V, Ljungberg P et al., PNAS 96;7962-7, 1999
Nephrin in CNF??

Kestilä, Lenkkeri, Ruotsalainen, Ljungberg et al., 1999

No nephrin – no slit diaphragm
Podocyte Gene Mutations known today

Gene control
- WT1
- LMX1B

Slit diaphragm
- Nephrin
- Podocin, CD2AP
- TRPC6

Cytoskeleton
- alpha-actinin-4
- inverted formin2
- myosin 1E

Podocyte

Cytosolic
- PLCe1
- mitochondrial COQ2, PDSS2
- lysosomal SCARB2

GBM
- Collagens A3-A6
- Laminin B2
Congenital Nephrotic Syndrome

- Primary forms:
  - Nephrin gene (NPHS1) mutations (CNF,NPHS1)
  - Podocine gene (NPHS2) mutations
  - Phospholipase C epsilon 1 gene (PLCE1) mutations (NPHS3)
  - Wilms tumor suppressor 1 gene (WT1) mutations (Denys-Drash, Frasier, isolated NS)
  - Laminin β2 gene (LAMB2) mutations (Pierson syndrome, isolated NS)
  - Laminin β3 gene (LAMB3) mutations (Herlitz junctional epidermolysis bullosa)
  - Lim homebox transcription factor 1β gene (LMXBI) mutations (Nail-patella syndrome)
  - Decaprenyl diphosphate synthase subunit 2 gene (PDSS2) mutations (Leigh syndrome with nephropathy)
  - Primary coenzym Q2 gene (COQ2) mutations (COQ2 nephropathy)
Etiology of NS in the first year

Monogenic disorders
(Podocytopathies)

- Nephrin (NPHS1, CNF) - isolated, severe NS
- Podocin (NPHS2) - isolated, steroid resistant NS
- PLCe1 (NPHS3) - isolated, early onset NS
- WT1 - Denys-Drash, Frasier, isolated NS
- Lamininβ2 (Lamb2) - Pierson syndrome, isolated NS
Etiology of NS in the first year

Genetic syndromes
- Mowat-Galloway syndrome
- Mitochondrial cytopathy
- Nail-Patella syndrome
- Glycosylation type I disorder
- Herlitz junctional epidermolysis bullosa

Familial (and sporadic)
- Gene defect not yet known
Treatment in less severe mutations

- Lahdenkari et al. Kidney Int, 2004
  - 25 adults MCNS as children
  - 5 NPHS1 heterozygotes
  - 1 Fin-major and Arg800Cys

- Schoeb et al. 2010:
  - 67 CNS/36 NPHS1
  - 3/11 steroids +
  - 9/34 ACE-inhibitors +
  - 8/28 ACE + indomethacin +
Should other medications be tried??

- Steroids, Cyclosporine ?? Not only immunosuppressants but also effects on the podocyte!!

- Probably no effects on primary mutation caused CNS, especially < 1 years of age. Severe mutations/less severe ones??

- Minimal change/FSGS no mutation and early infant CNS??

- Medications to reduce development of ESRD???
CNS; Recurrent Nephroses after Renal Transplantation

Kuusniemi AM et al., Transplantation, 2007
- 23 episodes/19 grafts in 13/65 pts. 1986-2006
- All Fin-major homozygotes, 73% anti-nephrin antibodies

Holmberg and Jalanko, Pediatr Nephrol, 2014
Diagnostics of CNS

- **Placenta**
  - > 25% of birth weight
    - Intrauterine proteinuria

- **Neurological findings (Mowat-Galloway, Pierson)**
  - Muscular hypotony common in NS
  - Microcephaly, seizures, retardation

- **Ocular findings (Pierson)**
  - Microcoria, embryotoxon, cataract, etc.

- **Genitals (WT1)**
  - Ambiguous

- **Cardiac findings**
  - LVH quite common in hypoproteinemia
  - Malformations reported in NPHS2 - patients
Renal biopsy

**Histology**

- Does not reveal the etiology

**NPHS1:** MI, FSGS, MCNS, DMS

**NPHS2:** FSGS, MCNS, CNF, MPGN

**WT1 and PLCe1:** DMS, FSGS

**Lamb2:** DMS

- Findings vary from glomerulus to glomerulus

- Tells about the progression
  - The amount fibrosis etc.

**Minimal change**

**FSGS**

**Mesangial increase (MI)**

**DMS**
Diagnostics of CNS (histology)

**Congenital**
- radial dilatation of PT  \(\text{NPHS1}\)
- MGC/FSGS  \(\text{NPHS2, NPHS1}\)
- DMS  \(\text{WT1, PLCE1}\)

**Infantile**
- MGC/FSGS  \(\text{NPHS2, NPHS1, WT1, PLCE1}\)
- DMS  \(\text{WT1, PLCE1}\)

**Childhood**
- MGC/FSGS  \(\text{NPHS2, NPHS1, WT1, PLCE1}\)
- DMS  \(\text{WT1, PLCE1}\)

**Juvenile**
- FSGS  \(\text{AR or Sporadic, NPHS2}\)
- AD  \(\text{ACTN4, TRPC6}\)
Gene analysis

**Diagnostics**
- Reveals etiology
- Guides for further studies
  - WT1: sex chromosomes, wilms’
  - Pierson: ocular and neurological studies

**Management**
- Genetic disorders resistant to immunosuppressives
  - Avoidance of unnecessary therapies
- Evaluation of the possible effect of therapy
  - “Mild mutation”: Missense (amino acid change)
  - “Severe mutation”: Deletion, non-sense, frame shift
Gene analysis

- Evaluation of the success of transplantation
  - Recurrence risk in the graft is low in genetic diseases
  - Choosing donor: LRD vs. CAD

- Genetic counseling
  - Prenatal diagnosis of the next child in the family
    - Analysis is fast if a mutation is already known

- Analyses available
  - Athena Diagnostics, Helsinki (Jalanko)
  - NPHS1 (nephrin), NPHS2 (podocin), WT1, Lamb2 (laminin),
  - α-Actinin-4, TRCP6
Nephrotic syndrome in the first year of life
Hinkes et al. 2007
CNS; Prenatal Diagnosis?
Patrakka et al., Lancet, 2002
CNS Summary

- Severe and mild primary forms
- Comorbidities important for long-term outcome
- Normal growth and development if early diagnosis and therapy and no comorbidities - Final height in boys -1.2 SD and girls -1.7 SD, normal puberty! (Tainio et al. Transplantation 2011)

- 25 years of pediatric transplantation in Helsinki (>400 pts, >200 kidneys - 100 CNS)

  doctors+patient
**Podocyte gene mutations**

- Induce injury to effects on the podocyte’s structure, actin cytoskeleton, calcium signalling and lysosomal and mitochondrial function
The Glomerular filtration barrier

PNAS, 2017
Oliver Smithies, Nobel prize 2007
NS Classification

- **Podocytropaties**
  - NPHS1, NPHS2, PLCE1

- **Syndromes**
  - WT1, LAMB2, TRCP6, PDSS2, ARGHDIA, LMX1B, OCRL, LAMB3
  - Galloway-Mowat

- **Secondary causes**
  - Infections
  - Immunological
  - Idiopathic NS
- 12-15% SRNS
- 50% ESRD
- FSGS
- 29.5% genetic
- >27 genes known
- no recurrence after Tx (other 10-50%)
Conclusions

- Nephrotic syndrome in an infant is rare
- Infections are possible and treatable cause in newborns
- Genes are responsible for NS in most infants
- Renal histology does not reveal the etiology
- Genetic testing is available and important
- RAS-inhibitors should be tried in most cases
- New drugs are needed