Junior Classes: Ciliopathies

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Overview of the lecture

• Definition, cilia structure, ciliogenesis, functions

• Disorders of primary cilia affecting kidneys:
  – Nephronophthisis related disorders

• Diagnostic approaches

• Summary
Definition

- **Ciliopathies** are a group of disorders caused by genetic mutations resulting in defective formation or function of cilium
  - multi-organ involvement
  - overlapping phenotype
  - growing number of identified genetic defects
    (ciliary proteome ~1,000 polypeptides)
First described in 1675 by the Dutch scientist Antoni van Leeuwenhoek in protosoa: cellular “little legs”. Cilium (Latin for eyelash) was coined by Otto Muller in 1786.
Ciliogenesis

Exit from cell cycle

Movement of mother centriole to the apical membrane

Extension of microtubules based axoneme to form cilia
  (microtubule formation, post-translational modification, actin dynamics, intraflagellar transport)

Wang & Dong AJP 2013
Alterations in post-translational modifications of cilia tubulins can cause disease phenotypes: CEP41 mutations encoding polyglutamase enzyme localized at the basal body cause Joubert syndrome (Lee et al. Nat genet 2012).
Cilia-associated cellular pathways

- Calcium signaling
- Wnt signaling
- Hedgehog signaling
- Notch signaling
- mTOR signaling
- Cell polarity and Planar cell polarity

- Cellular sensor (mechano-, chemo-, osmo-)
- Regulator of cellular growth and death
- Regulation of cell cycle

Wang & Dong AJP 2013
Primary cilia dyskinesia and Kartagener syndrome

- Disorder of motile cilia

- Prevalence: 1 in 15,000–20,000 individuals

- Recurrent sinusitis and low airway infections due to impaired mucociliary clearance, bronchiectases

- Situs inversus (Kartagener syndrome)

- Asplenia/polysplenia

- Congenital heart defects

- Reduced male fertility

- Genetically heterogeneous: most mutations affect dynein protein complex; autosomal recessive, but X-linked inheritance has been also reported
Altered motile cilia in Bardet-Biedl syndrome

- Defective cilia beat
- Similar phenotype in BBS 1, 2, 4, 6 knock out mouse models
- Role in patients’ phenotype?

Shah et al. PNAS 2008
Disorders of primary cilia affecting kidneys

- First link between ciliary dysfunction and kidney disease:
Nephronophthisis related disorders

- “Damage to nephrons”
- Most common genetic cause of renal insufficiency in children and young adults
- Incidence: 1: 50,000 life birth in Canada (Hildebrandt 2007)

- Autosomal recessive, genetically heterogeneous
  - NPHS1 gene is mutated in ~20% of the patients, other genetic causes are more rare; mutation detection rate ~30%
  - Most mutated proteins are located to the nephrocystin (NC) protein complex in the transition zone (regulates ciliogenesis and protein sorting)
  - Other cellular localizations have been shown (NC 1, 4, 8: tight junctions; GLIS2 and NC 2: nucleus and cilia; XPNPEP3: mitochondria)
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Abbreviation: MIM, Mendelian Inheritance in Man.
Clinical symptoms of nephronophthisis

- Moderate polydypsia and polyuria
- Secondary enuresis
- After 10 y.o.: growth delay, anemia
- Urine sediment: normal or mild proteinuria
- Renal ultrasound: normal or decreased kidney size, increased echogenicity, sometimes cysts
Renal histology in nephronophthisis

- Usually not required for diagnosis
- Interstitial fibrosis
- Tubular membrane disruptions (thickened, irregular)

Arts & Knoers Pediatr Nephrol 2013
Syndromes associated with nephronophthisis
Senior-Løken syndrome

• Ocular anomalies:
  – tapetoretinal degeneration
  – nystagmus
  – absent electroretinogram
  – vision loss
  – poor pupillary reflexes
Joubert syndrome

- **Central nervous system:**
  - Delayed psychomotor development
  - Ataxia
  - Hypotonia
  - Occipital meningocele (less common)
  - Hypoplasia of the brainstem, cerebellar vermis hypoplasia
  - ‘Molar tooth sign' on MRI cerebrum
1. Cerebellar vermis hypoplasia
2. Deepened interpeduncular fossa
3. Elongated superior cerebellar peduncles
Joubert syndrome, other features

- **Head**
  - Macrocephaly, prominent forehead, high, rounded eyebrows, low-set ears, anteverted nostrils, triangular-shaped open mouth, protruding tongue

- **Eyes:**
  - abnormal, jerky eye movements, oculomotor apraxia, coloboma of optic nerve, retinal dysplasia (less common), epicanthal folds, ptosis

- **Respiratory**
  - neonatal breathing dysregulation, episodic hyperpnea or tachipnea, central apnea

- **Hepatic fibrosis (less common)**

- **Skeletal (less common):**
  - Missing hand phalanges, postaxial polydactyly
Jeune syndrome

- Chest anomalies:
  - long, narrow thorax
  - short, horizontal ribs
  - bulbous, irregular rib ends
  - handlebar clavicles
  - pulmonary insufficiency
  - pulmonary hypoplasia
  - recurrent respiratory infections
Jeune syndrome, other features

- Liver: hepatic fibrosis, bile duct proliferation, polycystic liver disease
- Pancreatic fibrosis, pancreatic cysts
- Small pelvis, hypoplastic iliac wings, trident acetabular roofs, early ossification of capital femoral epiphyses
- Limbs: irregular metaphyses or epiphyses, short ulnae & fibulae, cone-shaped hand epiphyses, polydactyly, short phalanges, brachydactyly
Meckel-Gruber syndrome (MKS)

- **Kidneys & bladder:**
  - renal agenesis, polycystic disease, duplicated ureters, hypoplastic bladder

- **Central nervous system anomalies**
  - Anencephaly, cerebral hypoplasia
  - Arnold-Chiari malformation
  - Occipital encephalocele
  - Hydrocephalus
  - Dandy-Walker malformation
  - Cerebellar hypoplasia
  - Olfactory lobe absence
  - Absence of corpus callosum
  - Optic tract agensis
MKS, other features (1)

- **Head & neck**: microcephaly, sloping forehead, micrognathia, Potter-like facies, low-set ears, short or webbed neck
- **Eyes**: microphthalmia, hypotelorism, hypertelorism, iris coloboma
- **Mouth**: lobulated tongue, natal teeth macrostomia
- **Heart**: septal defects, coarctation of aorta, patent ductus arteriosus
- **Central closing defects**: cleft palate, cleft lip, cleft epiglottis, omphalocele
- **Pulmonary** hypoplasia
- **Biliary** tract bile duct proliferation, bile duct dilatation
- **Splenomegaly**, asplenia, accessory spleen
- **Single umbilical artery**
- **Intestinal** malrotation, imperforate anus
MKS, other features (2)

- **Genital anomalies**: small genitalia or ambiguous genitalia, cryptorchidism, separated vagina, uterine abnormalities

- **Skeletal anomalies**: postaxial polydactyly, syndactyly, clinodactyly, feet talipes
Bardet-Biedl syndrome

- Autosomal recessive (or digenic recessive)
- Renal anomalies (major), heterogeneous (NPH-like, ARPKD-like, ADPKD-like)
- Obesity
- CNS: developmental delay, learning disabilities (major), speech delay, ataxia, poor coordination
- Eyes: rod-cone dystrophy, onset by end of 2nd decade (major), retinitis pigmentosa, strabismus, cataracts
- Mouth: high arched palate, dental crowding, hypodontia
- Congenital heart defects, hypertension, LVH
- Hepatic fibrosis
- Hirschsprung disease (<10%)
- (Male) Hypogonadism (major)
- Polydactyly (major), brachydactyly

Diagnosis: 4 major features or 3 major and 2 minor features
### Human genes implicated in BBS

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<th>Chromosome</th>
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Bergmann Eur J Pediatr 2012
High arched palate

Dental crowding
Oro-facial-digital (OFD) syndrome

- **Inheritance**: X-linked dominant (lethal in males)
- Short stature
- **Head, neck, mouth**: microcephaly, facial asymmetry, microretrognathia, low-set ears, hearing loss, epicanthus, telecanthus, hypertelorism, downslanting palpebral fissures, broad nasal bridge, hyperplastic oral frenuli, buccal frenuli, lobulated tongue or bifid tongue (40-45%), tongue hamartoma (70%), high-arched palate, diverse dental anomalies
- **Cardiac** anomalies
- Fibrocystic liver (45%)
- **Pancreatic** cysts (29%)
- **Ovarian** cysts
- **Adult onset polycystic kidney** (50%)
- Abnormalities of the **fingers and tooth** (45%): clinodactyly, syndactyly, brachydactyly, polydactyly (rare)
- X-ray shows irregular pattern of radiolucency and/or spicule-like formation in metacarpals and phalanges
OFD syndrome, other features

- Skin milia of upper face and ears

- **Ectodermal dysplasia**: dry scalp, dry, rough, sparse hair, alopecia

- **Central Nervous System**: variable mental retardation (40%); central nervous system malformations (40%): abnormal gyrations, absence of corpus callosum, gray matter heterotopias, myelomeningocele (rare), stenosis of the aqueduct of Sylvius (rare), hydrocephalus, arachnoid cysts, cerebellar abnormalities; seizures; hypothalamic hamartoma, porencephaly, depression (rare)
<table>
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<tr>
<th>Phenotype overlap in renal ciliopathies</th>
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<tbody>
<tr>
<td><strong>Phenotype</strong></td>
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<tr>
<td>Renal cysts</td>
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<tr>
<td>Liver disease</td>
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<tr>
<td>Retinal degeneration</td>
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<td>Laterality defects</td>
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<td>Intellectual disability</td>
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<td>Polydactily</td>
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<tr>
<td>Obesity</td>
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<tr>
<td>Shortening of bones</td>
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<td>Ectodermal dysplasia</td>
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Diagnostic approach

- High level of suspicion (especially in patients with unclarified renal failure and normal urine sediment)

- Multi-organ involvement:
  - screen for eye, heart, abdominal organ, cerebral, skeletal involvement

- Perform genetic testing:
  - still many unidentified genes

- Genetic counselling:
  - The majority of disorders are autosomal recessive, but other modes of inheritance are possible

- Renal biopsy is rarely required
Summary

• Cilia are main cellular censors and regulators of diverse cellular processes

• Renal ciliopathies are the most frequent causes of renal insufficiency in children and young adults

• Phenotypic overlap between different underlying genetic disorders

• Genetic testing is important

• Treatment is symptomatic so far
Acknowledgements

D. Mekahli  
S. De Rechter

H. De Smedt  L. Missiaen  B. Van den Heuvel

Lab Pediatric Nephrology KU Leuven
Who was the first to described cilia?

Antoni van Leeuwenhoek (1632 - 1723)

Peter The Great (1672-1725)

Wolfgang Amadeus Mozart (1756 –1791)
Who is this?

Chlamydomonas Reinhardtii

Caenorhabditis Elegans
Which clinical features are NOT suggestive for a ciliopathy?

- Short stature
- Arthropathy
- Polyuria
- Diabetes mellitus
- Retinal anomaly
- Abdominal distention
Which protein is most frequently mutated in nephronophthisis?

- Polycystin 1
- Fibrocytstin
- Nephrocytstin 1
In which % of nephronophthisis patients DNA analysis reveals pathogenic mutations?

- 100%
- 80%
- 50%
- 30%
- 10%
Who is the professor?

Somebody who talks when others are sleeping....