Bedside skills-
Integration of clinical and bioinformatics tools in differential diagnosis

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Case history:  
A story of fathers and sons

Roger Martin du Gard, French Nobel laureate for literature (1937), described the death of an old man from renal failure in his 1929 instalment “The death of the father” of his novel “Les Thibaults”
Case 1: The father (1/2)

1958: Born. No perinatal problems
1976: Medical examination for military service. Erythrocyturia, otherwise normal except high-normal BP. Serves full term.
1981: Marries
1983: Birth of first son
1984: Repeated abdominal pains. Self-diagnosis flatulence, no visit to physician
Case 1: The father (2/2)

1986: Massive pain, massive erythrocyturia. Emergency hospitalization,

1993: Due to repeated erythrocyturia and malnutrition, surgical removal of the left kidney. The removed kidney weighs 5 kg (normal: 120-200g). Kidney function is reduced to about 50% of normal.


2002: Receives kidney transplant

2003: Episode of severe transplant rejection. Following repeated courses of immunosuppressive therapy, transplant function is stabilized at 35% of normal.
Case 2: The first son (1/2)


1986: Following the father’s diagnosis of kidney disease, the pediatrician initiates regular examinations. Physical examination, urin probes and ultrasound remain normal until age 10, when the regular check-ups are discontinued.

2001: Medical examination for military service. Erythrocyturia (microhematuria), otherwise normal. Due to family history, referral to nephrologist is ordered, and patient is banned from military service.
Case 2: The first son (2/2)

2001: Sees nephrologist.
Findings: Microhematuria. Kidney function: low normal range. Ultrasound: Multiple cysts, 1mm-1.5 cm diameter in both kidneys and liver.

Regular controls instigated.
Genetic counseling.
Case 2: The second son

1985: Born. No perinatal abnormalities.

1986: Following the father’s diagnosis of kidney disease, the pediatrician initiates regular examinations. Physical examination, urine probes and ultrasound remain normal until age 8, when the regular check-ups are discontinued.

2001: Following his brother’s diagnosis of PKD, sees nephrologist. No abnormal findings. Regular controls instigated. Genetic counseling.
Family history

Sister of index-patient (father): healthy.
Maternal side: No irregularities.
Paternal side: Maternal no irregularities.

Grandfather (born 1923) lived to age 61. Complained about fatigue, general weakness for many years. He always looked healthy, had quite a wide circumference, although he only ever ate small servings. His elder sister, born 1916, died in 1947 (aged 31) of “malnutrition”.

Great-grandfather died 1927 (aged 34) of “stroke”.

Elder generations/sidelines not known due to displacement during final war days.
Family tree

Stroke

Fatigue, large belly

Kidney cysts, Renal failure

Kidney cysts, Hypertension

Malnutrition?
About PKD (1/2)

Two inheritance patterns:

- **autosomal recessive** (prevalence= 1:10,000) with onset of renal failure in childhood,
- **autosomal dominant** (prevalence= 1:1000), adult onset of renal failure. 50% progress to end stage renal disease (ESRD). In Germany, about 8% of dialysis patients are due to PKD, in East Asia somewhat rarer.

The disease seen here is ADPKD.
About PKD (2/2)

ADPKD Pathophysiology: supersession of functional kidney tissue by cysts. The fetus shows already histological disposition for cysts, but frequently they become discernible by ultrasound only after about age 20 years. Cysts are due to localized increase in proliferation-enhancing substances that influence the epithelial growth, some proteins (polycystins) are defective.
Genetic basis of ADPKD

At least two different forms:

PKD2. 5-15% of cases. No co-segregation. Mutation most likely on Chromosome 4. Possibly better prognosis concerning development of renal failure.

PKD3. ? [http://ndt.oupjournals.org/cgi/content/full/14/12/2965](http://ndt.oupjournals.org/cgi/content/full/14/12/2965)

Many families show increased occurrence of (cranial) aneurysmata -> affection of pleiotropic genes!
Diagnostik measures (1/5):
family history

Family history is usually positive: spontaneous mutations are rare. False negative family history may be explained by alternate paternity (in Germany, about 4-8% of individuals).

Family history must include questions that go beyond “prevalence of kidney disease” as kidney failure may not have become obvious, or death/disease may be due to accompanying symptoms, such as intracranial bleeding following rupture of aneurysma.
Diagnostik measures (2/5):
imaging procedures: ultrasound

Abdominal ultrasound - sensitive in ~90% of affected patients at age 20.

Typical ultrasound image of PKD

Cyst after bleeding, ultrasound

Images from Koch, Klinische Nephrologie, München 2000
Diagnostik measures (3/5): imaging procedures: CT

Computer assisted tomography (CAT = CT) for special questions: definite detection of bleeding; pre-operative if nephrectomy is considered.

Typical CT image of PKD

Image from Grabensee, Checkliste Nephrologie, Stuttgart 2002

CT- image of horse-shoe kidney with PKD

Image from Koch, Klinische Nephrologie, München 2000
Diagnostik measures (4/5):
imaging procedures: CT demonstration

CT video copyright Klinik für Diagnostische Radiologie, Heinrich- Heine- Universität Düsseldorf, courtesy of Michael Fluess, MD.
Diagnostik measures (5/5): imaging procedures: MRI

Magnet Resonance Imaging (MRI = MR) for special questions: definite detection of bleeding; search for tumor within PKD cysts.

MR image of PKD. T1 scan. Cysts are more signal-intensive.

MR image of PKD. T2 scan. Bleeding is dark.

MR image of PKD. T1 scan. Bleeding is signal-intensive.

Images from Grabensee, Checkliste Nephrologie, Stuttgart 2002
Treatment

There is no specific treatment of PKD

Therapy tries to maximize the time before renal failure, and is symptomatic, aiming predominantly at blood pressure regulation.

If the polycystic kidneys become too large, the may lead to malnutrition, recurrent bleeding may cause anemia, infections and urolithiasis may have a health impact => surgical removal of one, sometimes both kidneys may become necessary.

Regular screening, as risk of cancer development is increased.
PKHD1 mutations, for example… (1/3)

Mutations on the PKHD1- gene on chromosome 6p cause the recessive form of polycystic kidney disease, ARPKD.

The longest continuous ORF is predicted to code for a protein of unknown function, wherein 63 mutations were known and suspected to play a role in disease severity (JASN 2003; 14: 76-89)

Bergmann et al. Poster T287 at WCN 2003
PKHD1 mutations, for example... (2/4)

Using DHPLC (denaturing high performance liquid chromatography), Bergmann et al. (RWTH Aachen) identified another 53 previously unreported mutations.

Bergmann et al. Poster T287 at WCN 2003
PKHD1 mutations, for example… (3/4)

More mutations were reported in the severe phenotype than the moderately affected phenotype.

Bergmann et al. Poster T287 at WCN 2003
PKHD1 mutations, for example… (4/4)
The type (truncating or missense) was more relevant for developing a severe phenotype than the location of the mutation.
Genetic counseling

Factors to consider:
- Frequency
- Inheritance pattern
- Phenotype variations
- Most important: the patient has the final say!
End of lecture….

…on to an organisatorial announcement!
Exam format for the topics from this series of lectures on Medical Informatics