Basic genetic examination

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Outline

• History
• Role of clinical genetics
• Genetic examination
• Genetic consultation
• Primary prevention
• Registries
• Summary
Historical milestones

J. G. Mendel – 1866: *Versuche über Pflanzenhybriden* (Experiments on Plant Hybridization)

William Bateson – 1905: *term GENETICS*

T. H. Morgan – 1933: *Nobel Prize for Genetic linkage study*

T. H. Morgan – 1944: *DNA is the carrier of the genetic information*

J. D. Watson, F. Crick, M. McCarty – 1953: *Structure of DNA molecule*
Chromosomes

23 chromosome pairs
Down syndrome

John Langdon Down – 1866
Observations on an Ethnic Classification of Idiots

Jérôme Lejeune – 1959
Etude des chromosomes somatiques de neuf enfants mongoliens
Cri du chat syndrome

Jérôme Lejeune – 1963
3 Cases of partial deletion of the short arm of chromosome 5
Molecular genetics

1985 - PCR reaction invented by Kary B. Mullis

1989 – CFTR gene mutation discovered by Francis Collins and Lap-Chee Tsui
1957 – One of the first departments of clinical genetics was founded at John Hopkins Medicine in Baltimore

today

McKusick-Nathans Institute of Genetic Medicine

Victor A. McKusick
1921 – 2008

www.omim.org
Clinical genetics (medical genetics) is an independent branch of medicine.

In the European Union the medical genetics is an individual specialization.

Departments of clinical genetics have their own laboratories and the clinical (ambulatory) part. Departments with their own beds are very rare.

The main goals of clinical genetics are as follows:

• Diagnosis
• Prevention
• Treatment
• Registration

The counseling should be strictly non-directive.
Most important diagnoses

Congenital Malformation is a congenital anomaly of the structure of some body part.

Birth Defect or Congenital Disorder are nearly synonyms for the term Congenital Anomaly.

Chromosomal Aberrations are the numerical or structural abnormalities of the karyotype.

Genetic Disorders are the conditions caused by the mutation of the gene(s).
Cooperation

**Pediatrics** (congenital anomalies, mental retardation, dysmorphic features, small stature, disorders of sexual development, metabolic disorders)

**Gynecology and obstetrics** (prenatal diagnosis, fetal abnormalities)

**Oncology** (hereditary cancer syndromes, oncocyto genetics)

**Neurology** (muscle dystrophies, epileptic syndromes, hereditary ataxias, hereditary neurodegenerative disorders)

**Internal medicine** (hemocoagulation disorders, hereditary diseases of the kidneys, hereditary cardiomyopathies and arrhythmias, hereditary forms of DM, hereditary jaundice, congenital immunodeficiencies etc.)

And others…

**Clinical geneticists provide counseling for other departments**
Indication for genetic examination

Prenatal

• abnormal results of prenatal screening (biochemical, combined)
• abnormal findings during prenatal ultrasound examination of the fetus
• higher age of the mother (35 years and more…)
• fetal death or spontaneous abortion in previous pregnancies
• congenital anomalies in the family history
• genetic disorders in family history
Indication for genetic examination

Postnatal

- Congenital anomaly
- Psychomotor retardation
- Sexual development disorders
- Abnormal growth
- Psychic disorders, autism
- Genetic disorder in family history
- Poor reproduction history (sterility / infertility)
- Multiple cancer diagnoses in family history
Indication for genetic examination

Preimplantation genetic diagnosis (PGD)

- Known genetic disorder in the family
- Exact mutation must be known
- Balanced chromosomal aberration in one of the parents
- IVF method is required
- Only the embryo without defect will be implanted
Genetic counselling

**Genetic counsel** is a special talk between clinical genetician and **proband**

**Proband** provides information about the problem (indication) and about family history (special forms are useful for collecting these information).

The other medical specialist **reports** are welcomed and sometimes **required**.

The genetician **informs** the proband about the (proposed) diagnose (or diagnose at risk) – clinical signs, prognosis, possible treatment, risk for other family members

The genetician **proposes** next steps (genetic diagnostics, prenatal tests)

**Genetician only informs** - It is up to the proband to decide!

It is recommended to give some extra time for proband’s decision.
Informed consent is an important part of clinical genetic practice

The agreement or disagreement of the proband with proposed test examination or procedure has to be confirmed by his or her signature.

The informed consent includes:

- Name of the procedure (test, examination...)
- The reason and/or indication for this procedure
- Possible alternatives to the proposed procedure
- Possible risks of the proposed procedure
- Proband's decision upon the future of the sample (DNA bank)
- Geneticists and probands declaration of validity of the consent
Genetic examination

Syndromologic examination is a very important part of clinical genetics practice.

The phenotype of the proband is examined closely and characteristic features are compared to the features of known genetic diseases and/or syndromes.

Dysmorphic features of certain syndromes can be very specific.

However, this process is very difficult and time consuming and the diagnosis are rarely made „on the first look“.

More specific tests are sometimes needed to confirm the proposed diagnosis

• Genetic tests (cytogenetic, molecular-cytogenetic or molecular-genetic)
• Other (Ultrasonography, MRI, RTG, ECHO, ECG, biochemical or hematological examination etc.)
Cytogenetics
Classical staining
G-banding
G-banding (CVS)
HRT
FISH

15p11.2 D15Z1
15q11-q13 SNRPN
15q22 PML

[Image of FISH result with chromosome visualization]
MLPA

Multiplex ligation-dependent probe amplification

Fluorescent dye
Forward primer sequence
Probe oligonucleotides
Stuffer sequence
Reverse primer sequence

Denaturation and hybridization
Ligation
Amplification

Target DNA

Methylated Target 1
Unmethylated Target 2

Denaturation and ligation
Ligation and digestion

Target 1
Target 2

PCR with universal primers X and Y

Only ligated probes are exponentially amplified

5’ X Y 3’

Fragment Analysis
Polymerase Chain Reaction (PCR)
Primary prevention

• The main goal is to **prevent** anomaly or malformation before they develop (that means before conception or during pregnancy).
• The women should avoid the pregnancy in very low or very high age. **The pregnancy should be planned.**
• The parents should avoid any contact with **mutagens** or **teratogens**.
• No stress, smoking, drugs and alcohol during pregnancy.
• Clinical geneticist should be consulted in advance – if necessary (repeated abortions, congenital anomalies in family, genetic diseases).
• Good compensation of mother‘s diseases (DM, PKU etc.)
• **Supplementation with folic acid**
Secondary prevention

• The main goal is to **prevent** the birth of a child with a congenital anomaly. However, the **termination itself is not a prevention**.
• We can terminate the pregnancy in order to prevent such a birth.
• However, the termination may not be legal in each country.
• In the Czech Republic it is legal to terminate the pregnancy because of severe genetic reasons **till 24th week** of pregnancy.
• Prenatal diagnosis is therefore very important, because we need the best information available about the condition of the fetus. If a severe condition is diagnosed, we may offer **termination** of pregnancy, prenatal **therapy** or **special treatment** in perinatologic period.
National Registry of Congenital Anomalies of the Czech Republic (NRCA)

- Unofficial monitoring in former Czechoslovakia started in 1961
- Official monitoring started on 1st of January 1964
- First stage (1964 – 1974) – only 36 selected diagnoses of congenital anomalies (CA) were registered
- Second stage (1975 – 1993) – 60 diagnoses of CA registered
- Present time: (1994 – now) – all cases in terminations of pregnancies (TOPs), stillbirths and live births are registered (age limit for reporting = 15 years)

Cooperating centre:
**Registration**

**Registry:** population based (whole area of the Czech Republic)

**Law:** The registration is compulsory, required by the Internal Law of Ministry of Health (nr. 14/2001). The database is run by the Institute of Health Information and Statistics of the Czech Republic

**Cases:** all cases in TOPs, live births and stillbirths (above 1000g) are reported

**Coding:** ICD-10 (international), no verbal description

**Sources:** Multiple sources, including departments of medical genetics, genetic laboratories, pediatric and neonatology departments, delivery units, ultrasound diagnostics departments etc.

**Termination of Pregnancy:** Legal, up to the 24th week of gestation (from genetic reasons)
Down syndrome – All cases in live births and prenatal diagnosis
Down syndrome

Down syndrome – relative number of prenatally diagnosed cases (%)
Number of invasive procedures needed for one diagnosis of Down syndrome
Prenatal diagnosis - Indications

Maternal age
Screening
Ultrasonography
Other

% Year

Spectrum of diagnoses – Prenatal diagnosis – All cases

- CA of neural tissue
- CA of cardiovascular tract
- Cleft lip and/or palate
- CA of urinary tract
- Diaphragmatic hernia and abdominal wall defects
- CA of bone and muscle tissue
- Chromosomal abnormalities
- Other
Maternal age – Time trends

% year

- 15-19
- 20-24
- 25-29
- 30-34
- 35-39
Clinical genetics (medical genetics) is an independent branch of medicine.

The most important diagnoses for clinical genetician are genetic disorders, chromosomal abnormalities and congenital anomalies.

The counseling should be strictly non-directive.

For the testing – the patient’s consent is required.

Not only diagnostics, but also prevention is very important.
Thank you for your attention!

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