THE STORY OF CYSTIC FIBROSIS IN PRAGUE

VĚRA VÁVROVÁ

on behalf of the

CF Centre Prague - Motol
CF IN PRAGUE (1946-1959)

The 1st CF case was diagnosed in May 1946

First publication on CF: Svejcar J, Benesova D, Houstek J: Cystická fibrosa pankreatu. Cas Lek Ces 1948;87: 1116-22

During 1946-59, CF was diagnosed in 25 infants and 1 child, all but one died at the mean age 0.49 years
In 1958 prof. Houštěk spent several months in the US. There he realised that a large proportion of children, who were treated for chronic pulmonary diseases, had in fact CF.

Thus, after his return he asked me to set up diagnostics and therapy of CF at the former Institute for Child Development Research.

My first task was to estimate the incidence of CF and to introduce the sweat testing for its diagnosis.
In the Central-Bohemian region, all deceased children were autopsied by prof. Benešová, who was interested in CF (in fact, she did not miss a single case with CF!). Together, we had reviewed all clinical and autopsy protocols within 1946-1960 and found that the incidence of CF was 1 in 2,730 livebirths.

Among the siblings of deceased children we also found one 11-year old misdiagnosed patient, considered to have “pulmonary fibrosis”
Sweat testing – “once upon a time”

In 1960 we started to use pilocarpine iontophoresis (Gibson and Cooke technique) by means of a "home made" device.

At the beginning, we measured chloride concentrations by 3 independent methods: manual titration polarography (1959 CZ Nobel P.) conductivity
Since 1976 we have utilised the commercial chloride titrator. Since then, our sweat testing facility has performed over 30,000 sweat tests. Nearly all of them have been performed by two technicians. Currently, the annual turnover has increased to 1,800 tests.

Statistical comparison of 4,974 controls versus 252 CF patients provided evidence that chloride concentrations over 31.5 mmol/L must be considered as borderline.
Sweat chloride concentrations in CF and controls (1985)
Neonatal screening - “once upon a time“

Test stripes for albumin with phenolphthalein blue were assessed between 1974-1975.

Meconium albumin analysis by immunoprecipitation method was performed between 1976–1977: 44,285 meconium samples were analysed and sweat test performed in 1,307 newborns - 8 had CF, but the false negativity was too high (33.3 % !). Due to low sensitivity and specificity we did not recommend this test for population-based screening.
Neonatal screening - “now”

Czech pilot study of the IRT/DNA/IRT scheme (2005-2006)

- Number of examined newborns: 76,438
- IRT in dried blood spots over the “cut off” (≥ 75 ng/ml): 800

- Number of diagnosed CF patients: 11
  - 10 of them had 2 CF-causing mutations
  - 1 of them had 1 CF-causing mutation and a positive sweat test
  - CF was diagnosed in 3 older sibs treated with other diagnoses
  - Negotiations are underway with the Czech Ministry of Health
Prenatal diagnosis - “once upon a time”

From mid-eighties we started with the examination of microvillar enzyme (GMT/GGT) concentrations in amniotic fluid.

We defined population specific range of normal and abnormally low values and started to offer this examination to families with 25% risk of CF.

In collaboration with Prof. D. Brock (Edinburgh) and Prof. A. Boué (Paris)
Already in 1989 our genetists started with RFLP analyses and in mid-nineties they reached >98% population specific detection rate of CFTR gene mutations.

Nowadays, in our CF cohort there is not a single patient with 2 unknown mutations and the small number of patients with one unknown allele decreases quickly due to international collaboration and introduction of novel methods (MLPA).
Biochemical studies

Helena Tomášová

Protease-antiprotease activity
Proteases were 3x more elevated in CF, while antiproteases (A1AT, A2M, TIC), also elevated, could not compensate their effect.

Circulating immune complexes
were elevated in *Pseudomonas aeruginosa* infected patients

Hypoxantine concentrations
correlated with the Shwachman score
CF and immunity

• no primary immunodeficiency in CF
• secondary changes in immune reactions due to the CF basic defect

Autoantibodies C-ANCA positive in a subset of patients

ANCA mediated inhibition of *P. aeruginosa* killing by neutrophils *in vitro*

Disbalance in cytokine production with negative influence on lung functions

TGFβ-1 as a disease modifying gene

Dendritic cells and infection with *P. aeruginosa*
Anthropometry and nutrition

Assessment of the nutritional status is performed at every clinical examination.

Longitudinal follow up of all patients

Mid arm circumference

Improvement due to modern therapy

Daniela Zemková

Božena Tomášková

Marie Nováková

Kyrthometry

BMI (SDS)

0
10
20
30
40
50
60
70
-3
-2.5
-2
-1.5
-1
0
1
3
8
10
12
14
16
18

SDS

Age

born < 75
born 76-85
born > 1.1.86
Lung function tests

Spirometry and oximetry is performed at every clinic

FEV\(_1\) and Median FEV\(_1\) in different age groups
PCR-based diagnostics and separation of patients had a beneficial effect on respiratory tract infections in children.
Physiotherapy

Respiratory physiotherapy

- Autogenic drainage
- Active cycle of breathing techniques
- PEP mask, Flutter
- Acapella choice
- Inhalation therapy
- Incentive spirometry
- Assisted AD, bouncing
- Physical exercise
Complications (1)

CFLD

Radana Kotalová

Cirrhosis 2.3% - 2 patients Tx

Meconium ileus
11.5%

Cardiomyopathy
18 patients
4 alive
1 of them after heart transplantation

Věra Hroboňová
Complications (2)

Stanislava Koloušková

CFRD

Regular oGTT screening since the age of 10 years

29.4% of adults

Osteoporosis

12.8% of adults
Czech CF Club

Psychological and social support for patients and families

“Marching with a Chick”: increasing awareness of CF

Auctions of patients’ drawings

Summer camps (cancelled due to infection control)

Weekends with parents

Helena Chladová

Tereza Tesařová

Kamila Šmídová

Alice Picková
Czech CF Registry

5 CF centres:
- 276 pts
- 35 pts
- 54 pts
- 17 pts
- 45 pts

EU Projects

www.ecorn-cf.eu

www.cfnetwork.be

www.eurogentest.org

www.eurocarecf.eu
1946 – 1959
26 infants diagnosed

1960: Sweat testing

1978: i.v. ATB treatment

1989: CFTR gene -> DNA diagnostics

1990: modern CF therapy

1995: rhDNase

1998: lung transplantation

Patient Cohort Prague

CF Centre Prague 1946-2007

664 patients

24 lost from evidence

347 alive at the end of 2007
66 of them in shared care
Influence of modern therapy on the course of CF

1. Before 1975; number of pts = 187
   Low fat diet
   Limited antibiotics choice
   Conventional physiotherapy (clapping)

2. Between 1976 - 1985; number of pts = 165
   Modern therapy since school age or puberty: 1978 - i.v. ATB
   1985 - preventive therapies
   1987 - Prolipase

3. Since 1986; number of pts = 287
   Modern therapy since early childhood: new forms of pancreatic enzymes, 1995 - rhDNase, better choice of antibiotics, nutritional support, modern physiotherapy.
   Since 1998 lung transplantation by the team of prof. Pafko in 20 CF patients
Age of patients

1998 vs 2007

Children
183 vs 184

Adults
68 vs.93

Kateřina Austová
(Pediatric nurse)

Božena Mottlová
(Adult nurse)

Libor Fila
Results of implementation of modern treatment schemes after 1990

Number of newly diagnosed patients and their survival steadily increases

Lung function ($FEV_1$)

Nutritional status (median BMI in SDS)

The overall quality of life has markedly improved!
CF patients and their “Prague doctors”
Due to political and socio-economic restrictions optimal treatment was **not accessible** to us prior to **1990**.

Since then, there has been **steady improvement** of:
- nutritional status
- pulmonary function
- quality of life
- **increased survival**
Personal conclusion: inspiration from CF families

CF life behind the Iron Curtain was rather difficult and often sad ...

Nevertheless, my personal life was enriched by meeting many wonderful and brave people suffering from CF!

Nowadays, I am happy to work within a comprehensive CF team that provides specialised care to them, equivalent to that in developed EU countries.

Let me express my deepest gratitude to them - they showed me true life values and inspired me all the time!
Thank you for your attention!

... and to ECFS once again for giving me the

"2008 Award"