# Diagnosis and treatment of ADA deficiency - first patient diagnosed in Czech Republic

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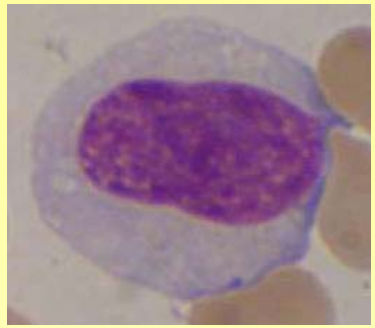
HSCT
UNIT - PEDIATRICS

PRAGUE
CZECH REPUBLIC

# Adenosine deaminase (ADA) deficiency



- initially described in **1972**
- 15% of SCID
- **T-B-NK- SCID**
- **AR** disorder of **purine metabolism**
- **the absence of ADA**

  an accumulation of toxic metabolites

  impairs lymphocyte differentiation, viability and function
- erythrocyte ADA activity
- 60 mutations in the ADA gene

# ADA deficiency – clinical and laboratory types

- **80% patients – early-onset**
  - within the first 3 months
  - < 0,01% ADA activity, ALC < 100/mm$^3$
  - severe hypogammaglobulinemia
  - hepatic, renal, neurological, skeletal abnormalities, hearing loss
- **15-20% - delayed-onset**
  - at the age of 1-2 years
  - 0,1-2% ADA activity, ALC < 500/mm$^3$
- **5% - late-onset**
  - at the age of 3-15 years
  - 2-5% ADA activity, ALC < 800/mm$^3$

# ADA deficiency - therapy

- stem cell transplantation (id. sibling or MUD)
- ADA-replacement therapy
  PEG-bovine ADA since 1986
- gene therapy of hematopoietic cells

# Family and past medical history

- boy, 4 month old at diagnosis of ADA deficiency

FH: parents first line cousins (Gipsies-Romany)

PMH: from 3rd pregnancy (2 miscarriages)
delivery in 38th week, 2350g/44 cm,
adaptation after delivery normal
BCG vaccination administered

- respiratory and skin infections from 3 weeks
- failure to thrive from 2 months

# 3,5 months of age

- admission to pediatric department
- oral candidiasis, bronchitis, diarrhea
  (dyspeptic E. coli, rotaviral infection)
  therapy with ATB, antimycotics
- severe lymphopenia (ALC 1040/μl)
- T, B, NK cells depletion
- severe hypogammaglobulinemia

- susp. SCID – transfer to our hospital

## 4 months of age (August 3, 2005)

# Clinical and laboratory findings

- palor, **hypotrophy** (weight 3,22kg, length 52,5cm), fever
- WBC $9x10^9/l$, Hb 105g/l, Plt $351x10^9/l$
- **ALC 900/µl**
- **IgG 0,58, IgA<0,067, IgM <0,042g/l, IgE <1 IU/ml**

- **CD3+ 2%, abs. 0,02**
- **CD4+ 1,5%, abs. 0,01**
- **CD8+ 0,8%, abs. 0,01**
- **NK cells 25%, abs. 0,23**
- **CD 19+ 1,7%, abs. 0,02**

## SCID T-B-NK-

# ADA deficiency

- the absence of ADA activity in erythrocytes and the accumulation of toxic metabolites (urine deoxyadenosine)
  *(Inst. of Inherited Metabolic Disorders, Prague)*

- homozygosity for mutation 905C>T; S302F (both parents are heterozygous for 905C>T)
  *(Correlagen Diagnostics, Cambridge)*

- no maternal engraftment, no signs of BCG infection
- malformation of Th5 vertebra
- no CNS, hepatic, renal involvement

# Therapy

- **no suitable donor for SCT was available**

- **indication for replacement therapy with PEG-ADA (2-3 months) and then for gene therapy**

*(San Raffaele Telethon Institute for Gene Therapy, Milan)*

- ADA-GEN, Orphan Europe started on August 30, 2005
- 30IU/KG/dose twice a week (intramuscular injection)

# Clinical outcome

- **antibiotics** (claritromycin, gentamycin, ciprinol, meropenem)
- **antimycotics** (flukonazol)
- **antituberculotics** (INH, RIF)
- **trimethoprim, corticosteroids, IVIG**

- **progressive bilateral interstitial pneumonitis hyposaturation, tachypnea - oxygenotherapy**

- **microbiological, serological** (influenza, parainfluenza, RSV, ADV) **and PCR** (CMV, EBV, ADV, HHV6, mycoplasma, chlamydie, RSV) – **negative**

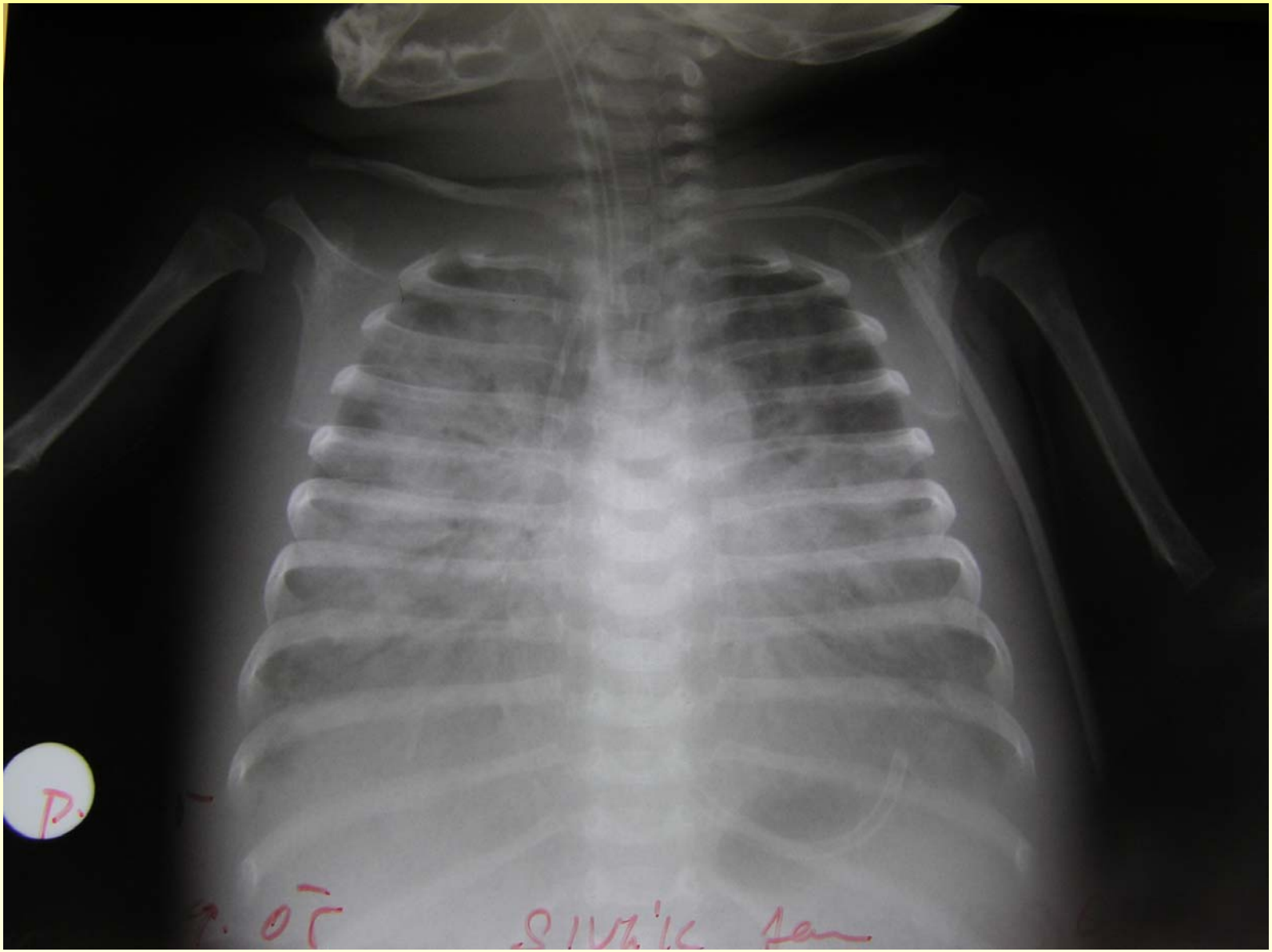
- **progressive respiratory insuficiency**

→ **arteficial ventilatory support (Sept. 8, 2005)**

# ICU

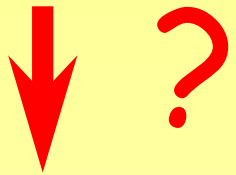
- **continuing ventilatory support with high FiO2, NO and oscilation ventilation**
- **continuing treatment with ADA-GEN**
- **wide-range antibiotics** (claritromycin, ciprinol, amikin, teicoplanin), **antituberculotics** (RIF), **antimycotics** (fluconazol), **trimethoprim and virostatics** (GCV, palivizumab), **IVIG**
- **progressive respiratory insufficiency with pneumonitis of unknown origin (all cultures, virological and PCR tests remained negative)**
- **died on September 24, 2005**

# X – RAY Sept. 19th, 2005



# ADA activity and dAXP - summary

- **newborn screen blot** (6.4.05)
  %dAXP: 43.7 (n. 0-4)
  *Duke University Medical Center (prof. M. Hershfield)*
- **at diagnosis** (4.8.05)
  ery-ADA activity: 3 nM/h/mgH (n. 13-89)
  U-deoxyadenosine: 236 mM/ml Kr (n. undetectable)
  *Prague*
- **at start of PEG-ADA** (30.8.05)
  ery-ADA activity: 6.56 U (n. 8-16 U) – after blood trf.
  plasma-ADA activity: 0.31 U (n. 30-60 – on PEG-ADA th.)
  *San Raffaele Telethon Inst. for Gene Therapy, Milan*
- **on PEG-ADA therapy** (12.9.05)
  plasma-ADA activity: 58.3 nmol/h/mg (control 15.3)
  dAXP: undetectable
  *Duke University Medical Center (prof. M. Hershfield)*



- **PEG-ADA within an effective range for correcting metabolic abnormalitis due to ADA deficiency**

  (significant response in metabolic abnormalities correction – at least 6-8 weeks of treatment)

- **blood cultures 5 days before death positive for multiresistant Pseudomonas aeruginosa (treated with sensitive atb)**

- **autopsy: bronchopneumonia haemorrhagiconecrotica diffuse and bilateral, at left lower lobe fungal infection (Aspergillus spec. v.s.)**

# Conclusions

- pneumonitis without any clear pathogen is not uncommon in patients with ADA deficiency

- toxic pneumonitis due to ADA deficiency ??? epithelial damage ?

- mycotic and bacterial infection in severe immunodeficient patient ?

# Thank you for attention