Unknown combined immunodeficiency with T cell lymphopenia

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Medical history

- X.Y., male, DOB: 26.02.2000
- the second child, non consanguineous parents.
  Maternal uncle's son – CF in susp., sweat chlorine 65 mmol/l, genetic testing not confirmed CF.
- normal gestation, birth weigh - 4250 g, hight 55 cm.
- Vaccinations: BCG, HB1 at birth,
  $DTPa_{1\text{-}2\text{-}3\text{-}4}$+$IPV_{1\text{-}2\text{-}3\text{-}4}$, $Hib_{1\text{-}2,}$ DT_5, OPV_5, HA from 2 year old without complications.

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- At the **2 weeks** of age – **pemphigus neonatorum**;
- **5 months** - **sepsis**: pneumonia, enterocolitis, **hepatosplenomegaly**, mucocutaneus fungal infections, piodermia. (*Staph.aureus* from the pus and stool culture)
- **6 months** - **sepsis**: toxic-septic shock, bilateral pneumonia with r. atelectasis S $_{6, 9, 10}$, DIC syndrome, liver's abscess in susp.

  (mechanical ventilation for 2 weeks and non irradiated blood component's transfusions (EM, TM, plasma);

  (*Staph. aureus, Pseudomonas aeruginosa, Str. pneumonia, Candida sp.* from intubation tube).

An.morbi

- **7-8 months**

  - **pneumonia** with bronchial obstruction and pur. mucus,
  - **hepatosplenomegaly**.

- **10 months** – **cystic fibrosis** due to recurrent chest infections, viscid mucus in the small airways, malabsorbtion, failure to thrive, cholestasis. (*Moraxella cath., Strept. α hemolyticus, Candida* from BAL)

- **1-2 years**

  - recurrent fevering, repeated episodes of cough with purulent sputum, persistent changes in the right lung,
  - **cholestatic hepatitis**, **hepatosplenomegaly**.

  Portal hypertension was excluded by sonography, EGDF.

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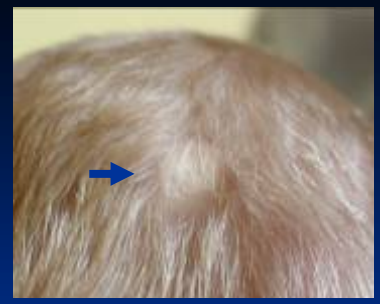
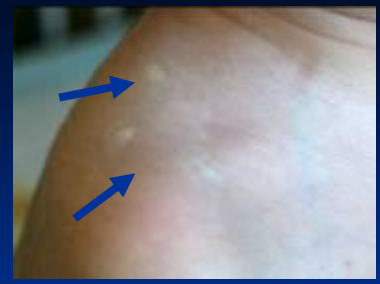
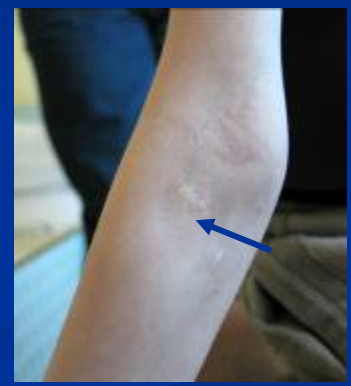
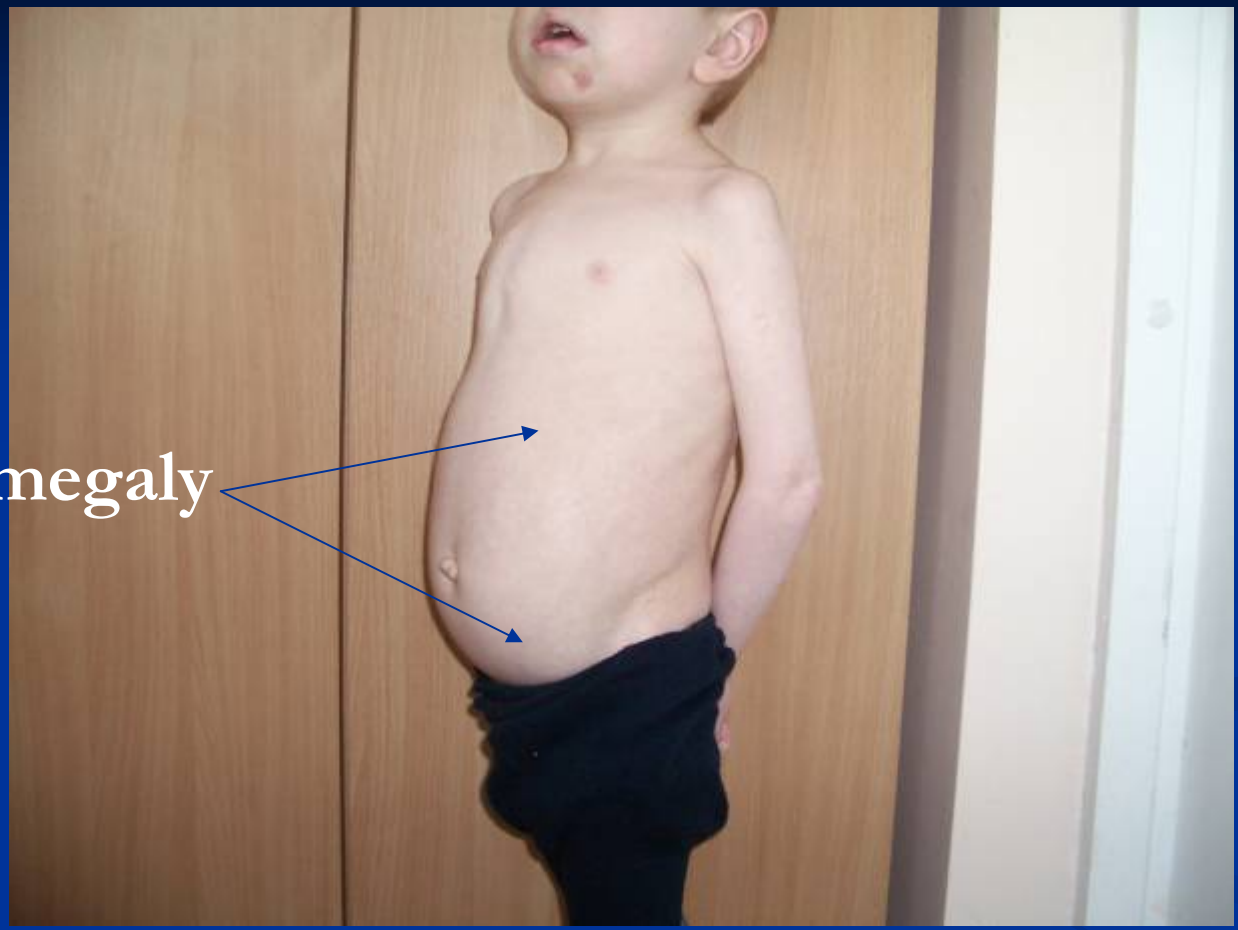
- **2-3 years:**
- **recurrent purulent skin diseases,** flegmona, furunculosis (*Staph.aureus*) prolonged wound healing,
- **2 episodes** of **bone fractures, hyperextensibility,**
- gingivostomatitis (*Candida sp*),
- **rec. pneumonia** (*Strept. pneumonia, Moraxella, H. influenza*)







- **4 - 5 years:**



- **Splenomegaly**

The **spleen biopsy** (5 years) histology:

- reactive hyperplasia of lymphoid follicles,
- signs of splenitis,
- extramedular focus of haemopoesis.

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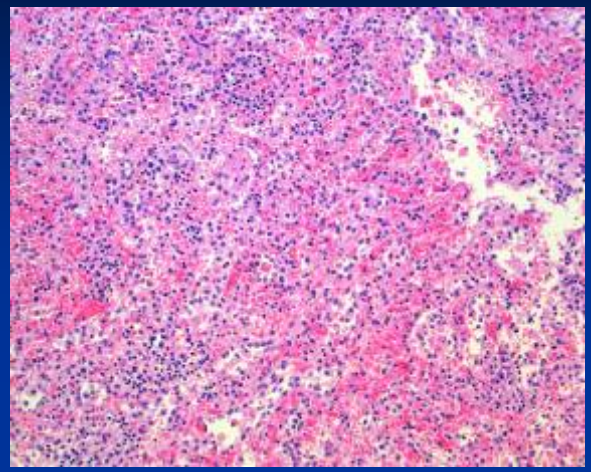
- **5 - 6 years:**
- chr. diarrhea (steatorrhea, lactose intolerance),
- mucositis, esophagitis *(Candida sp.),*
- urinary tract infection *(E.coli, Klebsiella pneumonia),*
- pneumonia (*Moraxella, Staph.aureus, Pseudomonas aeruginosa IBL, Strept.pneumonia, Staph. epidermidis*, fungal in susp.)

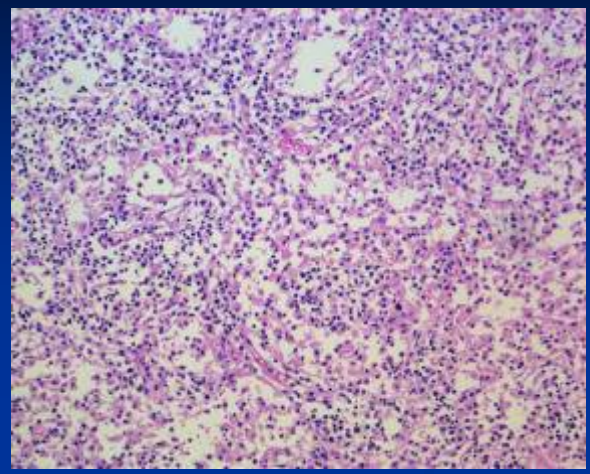
- **6 y: sepsis:** enterocolitis *(Pseudomonas aeruginosa IBL, Candida, Campilobacter jejuni*), bilateral polisegmental pneumonia, otitis, DIC syndrome, hepatosplenomegaly (fatal outcome).

Patanatomical findings

Spleen



Lymphnode

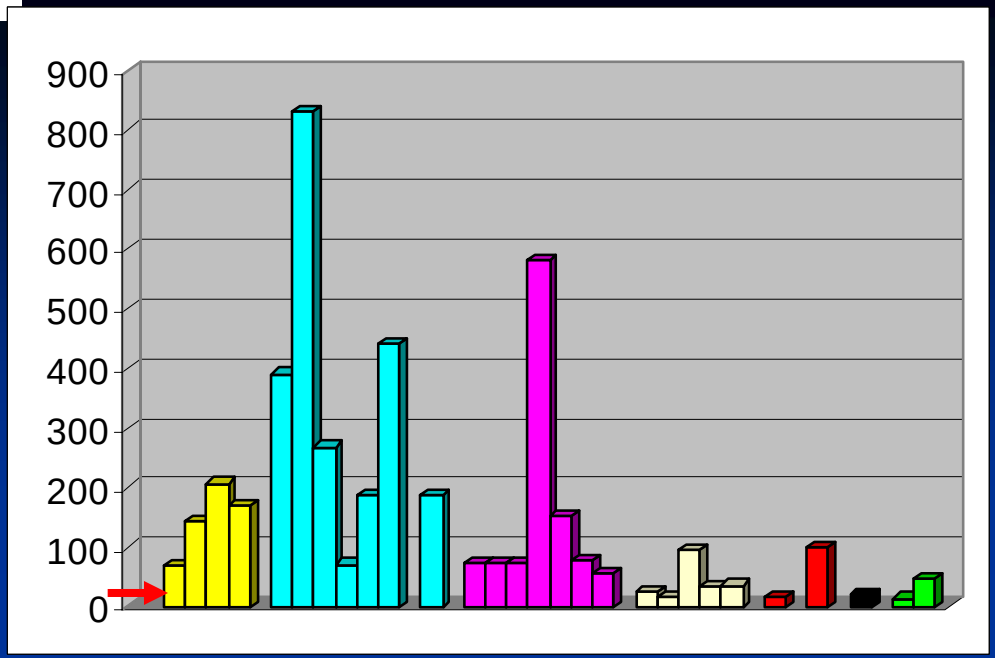


- ***Mb. princ.:***

  Primary combined immunodeficiency (D81.9).

- ***Complications:***

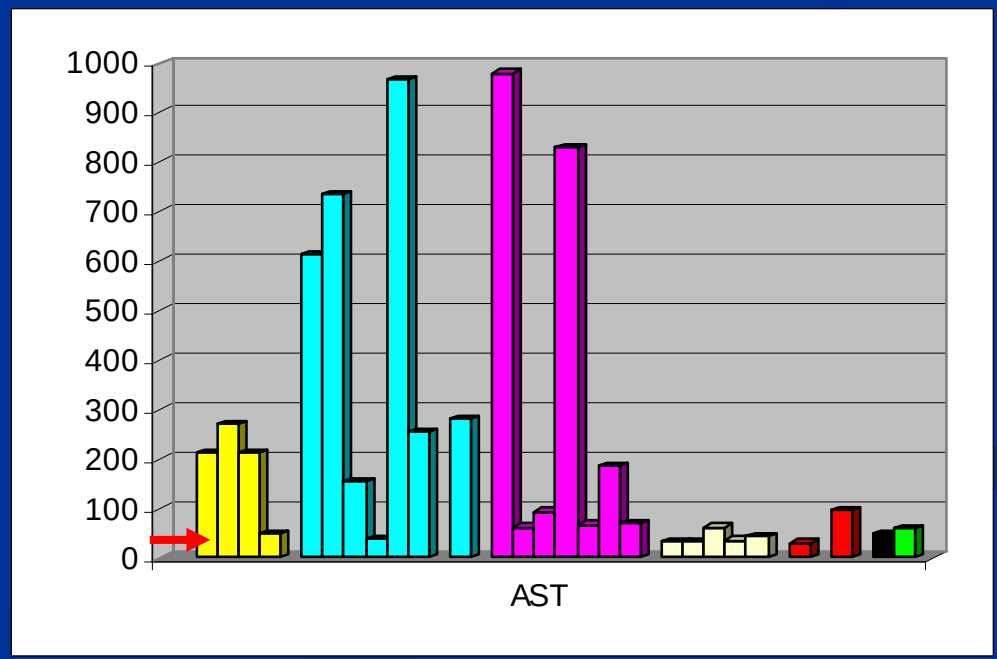
  Sepsis: bilateral pneumonia, r. lung's abscesses, non exudative pleuritis, diffuse alveoles' lesion syndrome, oesophagitis ulcerosa, ulcerated enterocolitis, splenomegaly. Hepatic cirrhosis.



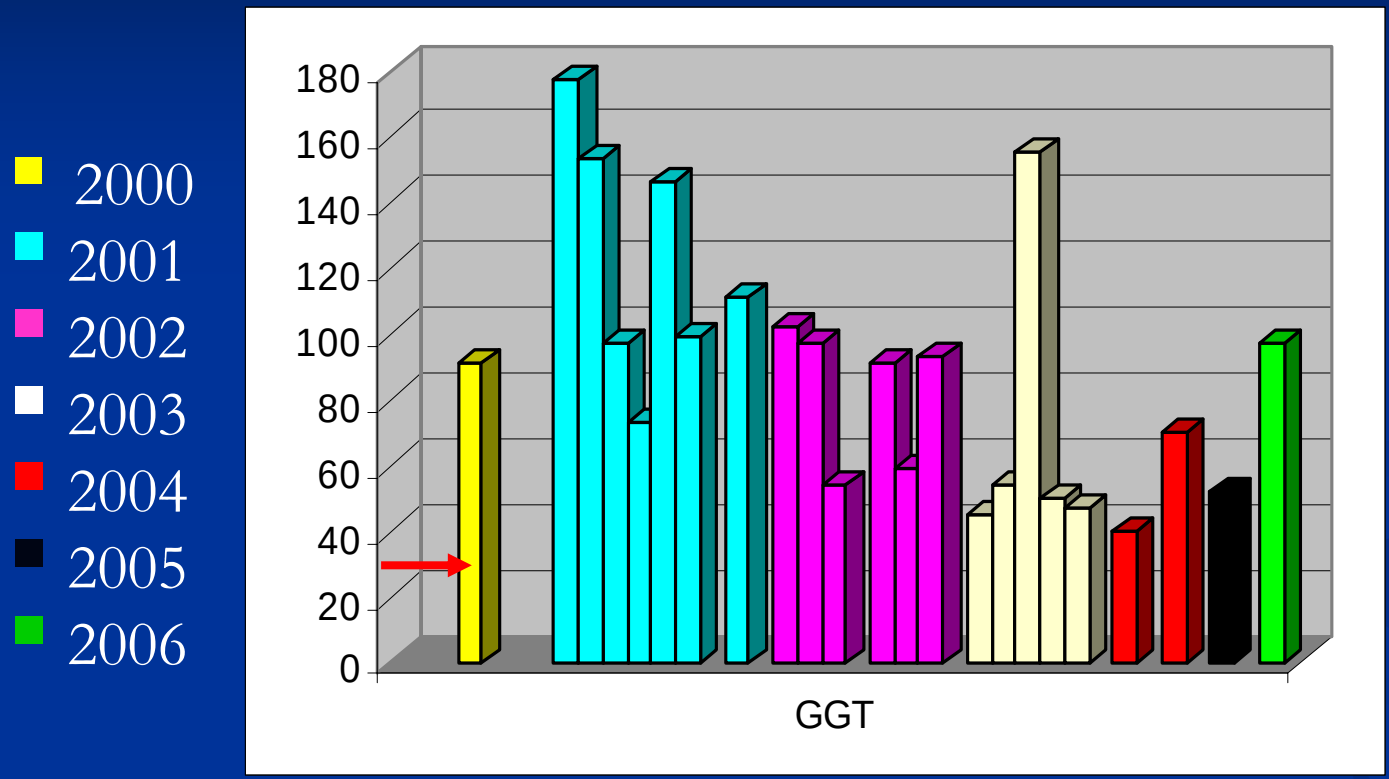
ALT

AST

- 2000
- 2001
- 2002
- 2003
- 2004
- 2005
- 2006



γ-GT



Alkaline phosphatase (AP) level was normal (N: 250-950 U/L)

Serum bilirubin levels were normal, except one episode of increased total and direct bilirubin at 2 year old (2002). (TB- 56,4; DB-21,9 mmol/l, N: <17/<4,5)

Abdominal US

- **6 month** - enlargement of liver, increased echogenicity, regular surface, normal vascularization. Hypodensic focuses, ~1-2 cm in diameter with fluid inclusions in the right hepatic lobe.
  - **CT**: A hypodensic focus, ~1.6 x 0.7 cm in diameter, was seen in the right hepatic lobe by CT. Liver's ducts not dilatated.

- **1 - 5 year** of age - nonhomogenous internal liver's structure, v.portae branches were infiltrative, increased echogenicity of intrahepatic ducts' walls. Splenomegaly.
  - EGDF – normal. Sonography of v. portae system – **PH excluded** (2001.12).

- **6 year** of age - hepatomegaly - right lobe 13,0 -17,4 cm (N: 6,0-7,4 cm), increased echogenicity, nonhomogenous structure; splenomegaly -147- 200 mm (N: 49-58 mm), homogenous structure. Ascites.

Laboratory analysis

- Sweat chlorine 47 mmol/l (N)
  CF genetic testing: F 508 del (-) (R 553X, G542G, G551D, H 1303K, CFTR dele 23 (21 hb) will be done)
- Normal α-1 antitrypsin level 2,2 g/l (N:0,9-2,0 g/l).
- Bone marrow investigation – normal.
- Total protein level: 71-52-61-67-57 - 37g/L (N: 66-83),
- Albumin 29,2 g/l (N:38-54).
- α amilase 57 U/L (N:0-220)
- CK 163 U/L (N:24-170)
- LDH 2966-997-615 U/L (N<1100)
- K^+, Na^+, Ca^{++}, Cl^- , glucose – normal.

Laboratory analysis

- Serology for hepatitis A, B, C, HSV, HIV(-),
- toxoplasmosis (-),
- CMV IgM (-), IgG (+)(1.16, pos.> 0.2),
- RPR screening test negative.
- Mantoux test negative.

- anti-dsDNR (-), CIC (-)
- A (II), Rh D+, D.Coombs test positive.

- Bacteriologically:

Staph. aureus,

Pseudomonas aeruginosa,

Str. pneumonia,

H. influenza,

Klebsiella pneumonia,

Campilobacter jejuni,

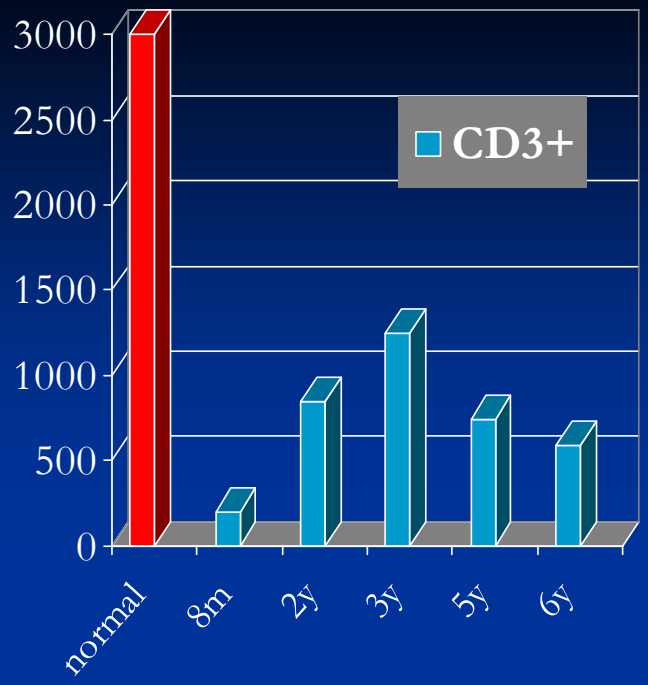
Candida sp.

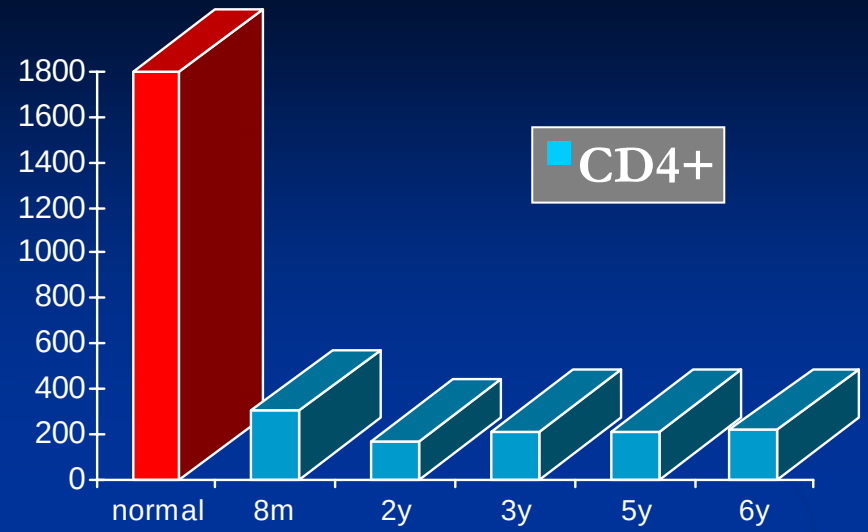
Laboratory analysis

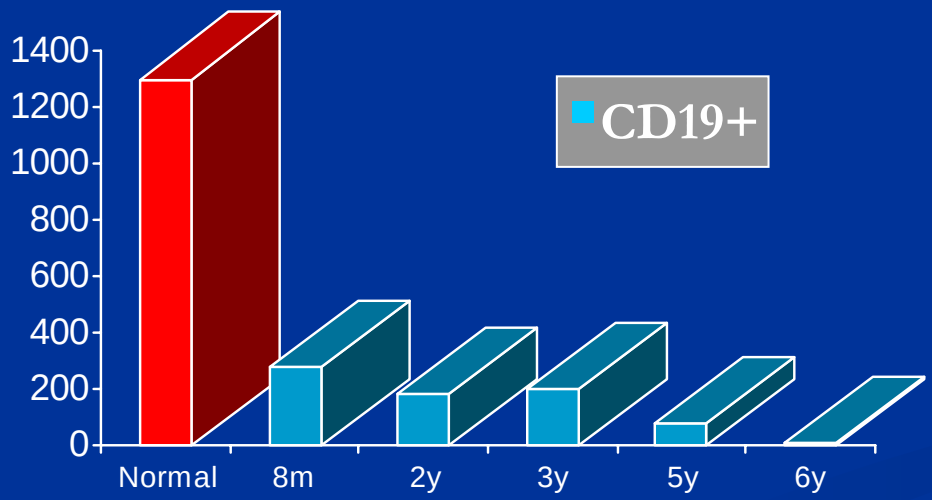
- WBC: 6.9- 14.1- 3.4- 20.6 (max)- 4.3- 12.0- 5.5 ..- 2.3-1.7-3.9 x109/L,
- lymphopenia (27- 31- 31- 24.6- 23- 16.4 -15.. – 17-11-6% /0.82..-0,2 $x10^9$),
- normal eosinophil count,
- PLT: 83 to 238 $x10^9$/L,
- anemia (Hb 131-62-123-59-114-107 g/L, decreased MCV, MCH),
- decreased level of serum ferum (1.5 mmol/L).

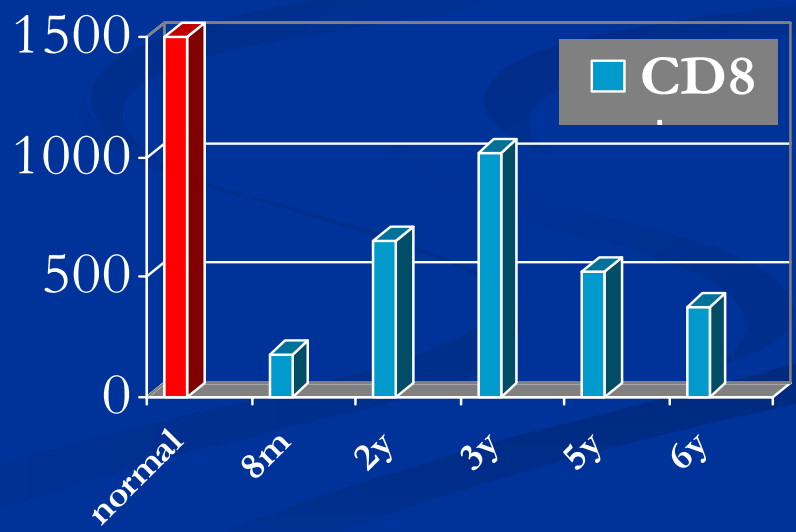
Lymphocytes' subpopulations

Parameter	Result 18.10.2000 / ~7m. old		Result 29.01.2002 / ~2y old		Result 26.02.2003 / 3y old		Result 28.01.2005 /~5y old		Normal value 1-6 y
Absolute lymphocytes count		819		1156		1520	23	828	38-53% / 2900-5100 mm^3
CD3+	61	199	73	844	82	1246	89	737	62-69% / 1800-3000 mm^3
CD3+CD4+	37	303	15	173	14	213	26	215	30-40% / 1000-1800 mm^3
CD3+CD8+	22	180	56	647	67	1018	63	522	25-32% / 800-1500 mm^3
CD4/CD8	1,68		0,27		0,21		0,41		1,0 – 1,6
CD16+/CD56+	7	57	7	81	7	106	2	17	8-15% / 200-600 mm^3
$CD19^+$	31	278	16	185	13	198	9	75	21-28% / 700-1300 mm^3
$CD3^+/CD25^+$	3		2		4		2		8-12%
CD3+CD45RO+ (naïve)							73		
CD3-CD45RO							3		
CD3+CD45RA+(memory)							30		
CD3-CD45RA							7		

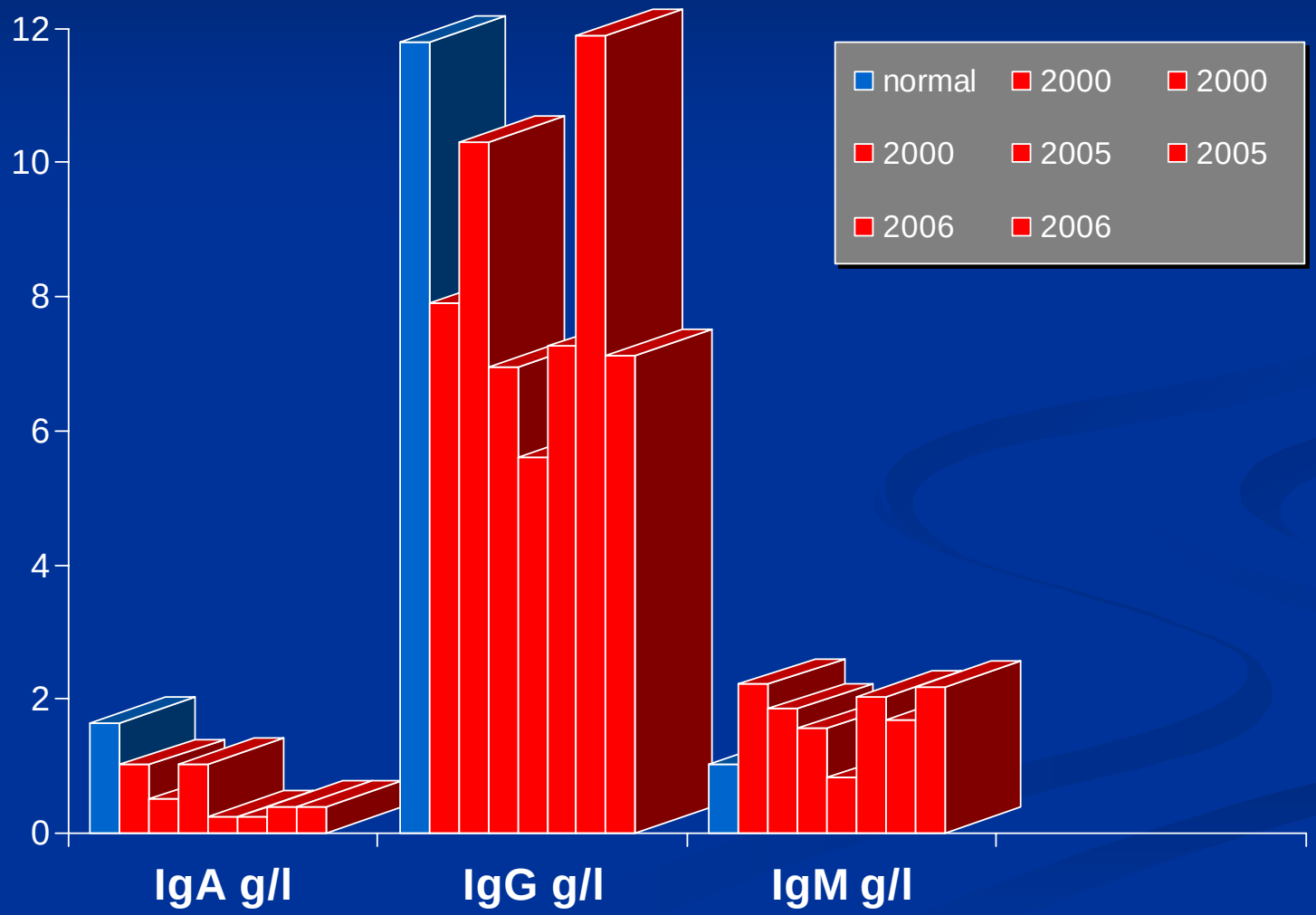

3000
2500
2000
1500
1000
500
0
CD3+
normal
8m
2y
3y
5y
6y


1800
1600
1400
1200
1000
800
600
400
200
0
CD4+
normal
8m
2y
3y
5y
6y


1400
1200
1000
800
600
400
200
0
CD19+
Normal
8m
2y
3y
5y
6y


1500
1000
500
0
CD8
normal
8m
2y
3y
5y
6y

Immunoglobulins 2000-2006 y



Lymphocytes' proliferation, NBT

Parameter	~7m. old	~2y old	3y old	~5y old	Normal value 1-6 y
Lymphocytes transformation test against PHA	-	37	31	3	30-40%
Lymphocytes transformation test against PWM	-	-	3	3	8-10%
Lymphocytes transformation test against tuberculin	negative	-	7	n.i.	negative (< 5%)
Neutrophyl respiratory burst spontaneous	50	40	-	16	15-25%
Neutrophyl respiratory burst PMA stimulation	36,5	43		93	45-65%
Neutrophyls' activity with latex's particles				76	15-20%
CIC			0,045	0,037	< 0,08

Discussion. Diagnosis?

- **PID *(T cell deficiency)* –**

- sepsis (umbilical?), toxic-septic shock, vein thrombosis ? -

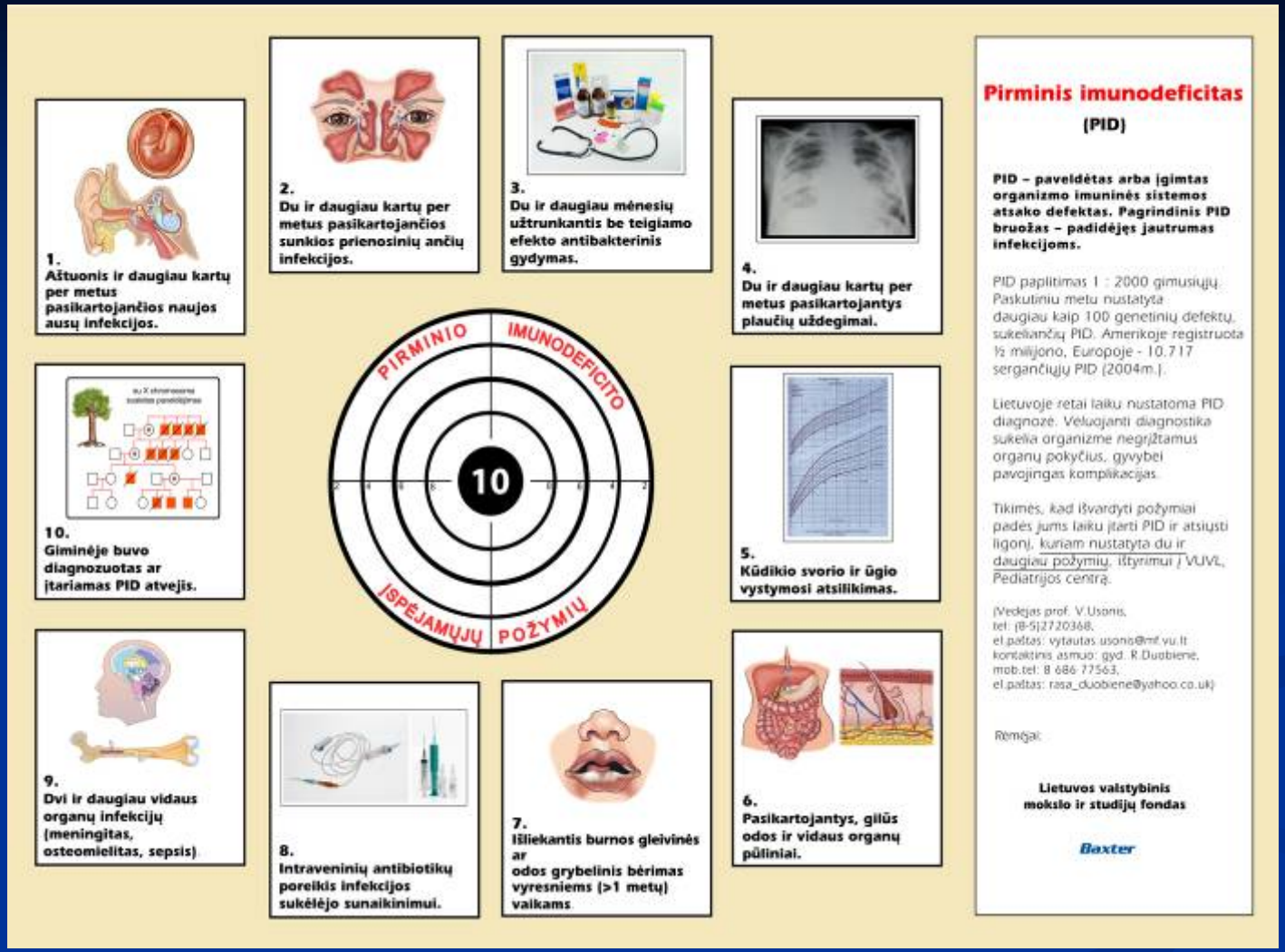
- portopulmonary hypertension - splenomegaly -

- persistent cholestatic hepatitis - hepatic cirrhosis -

- sepsis.

- **or secondary ID** (*cystic fibrosis, liver disease…*) **?**

- What's your comments?



Thank you for attention

CD3⁺HLA-DR	**8**	**65**	**5**	**58**	**28**	**246**	**44**	**364**	**6-16%**
(CD14+)HLA-DR⁺	**57**		**56**		**87**				**65-85%**
CD3⁺/CD25⁺	**3**		**2**		**4**		**2**		**8-12%**
CD3⁺/CD71⁺							**27**		***1,5-2,0%***
CD3⁺/CD54⁺							**68**		***2,0-4,5%***
CD3⁺/CD69⁺							**10**		***1,0-2,0%***
CD3⁺/CD11b⁺							**57**		***20-40%***
CD3⁺/CD57⁺			**0**				**3**		**2-5%**
CD8⁺/CD57⁺			**2**				**48?**		**6-15%**
CD8⁺/CD38⁺							**59**		***5-9%***
CD8⁺/HLA-DR⁺							**51**		***3-5%***
CD4⁺/HLA-DR⁺							**18**		***3-5%***