Proposal for Central European Register for Patients with CGD

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CGD Genetics

- Recent reports of mutations in CGD patients
  - Latin America:
    - Agudelo-Flórez et al. in *Pediatr Blood Cancer* (2006) described 14 LA patients (9m, 5f: 7 X-CGD – 2 novel mut.; 7 A47-CGD all ΔGT del.)
    - Barese et al. in *J Pediatr Hematol Oncol* (2004) described 18 Argentinean patients (all male X-CGD – 7 novel mut.)
  - Asia:
    - Ishibashi et al. in *Hum Genet* (2000) described 33 mutations from 229 Japan CGD patients (28 X-CGD – 18 novel mut., 5 A22-CGD all new mut.; 48/109 X-CGD and 5/16 A22-CGD)
    - Reports from Korean and Chinese patients

CGD Genetics

- Europe: genetic mutations epidemiology of CGD patients from different West European countries (Sweden, Netherlands, France, Italy, Spain, Germany, Switzerland)

- Eastern Europe:
  - Jurkowska M et al. (2004): **The search for a genetic defect in Polish patients with chronic granulomatous disease.**

    described 6 X-CGD patients with 4 different (1 novel) mutations in CYBB gene and 2 patients with typical GT deletion in the NCF1 gene (1 had additional unique mutation)

Objectives

- Analyze clinical and genetic features in Central European CGD population
- Investigate genotype - phenotype correlation
- Compare features of CE CGB population with other CGB patients

Methods

- Assemble data from CGD patients from Central – Eastern Europe (Countries involved in J Project and other interested countries form area)

- CGD – Genetics Questionnaire

CGD – genetics Questionnaire

University Children Hospital
Ljubljana, Slovenija
Vrazov trg 2, SI 1525
Tel.

Patient INFO

Visit date: 17.4.2007

DNA sample taken: 10.4.2004

Patient ID	SIAS110786	Sex (male/female):	M
Date of birth (DD-MM-YYYY)	11.07.1986		
Height: 162,5cm		Weight: 45,2kg	
Ethnic background:	Father: Caucasian	Mother: Caucasian	
Familial case:	Yes	older brother	
Country of residence:	Slovenija		

Ethnic background: Please indicate ethnic groups of parents (Caucasian, Black, Asian, Indian, Mixed)

Familial case: Please indicate if there is another patient with CGD in the family (yes/no/unknown) and who is it.

Diagnosis:

Date of diagnosis (DD-MM-YYYY)	…11.1986
Onset of symptoms (DD-MM-YYYY)	…11.1986

Genetic tests already performed (yes/no): yes

Date (DD-MM-YYYY)	Genetic test	Result
14.4.2004	Sequence analysis of CYBB	290: CGA→TGA; Arg290stop

Clinical and pathological manifestation of CGD:

Date (MM-YYYY)	Infection	Infectious organism	Hospitalization	
			Yes	No
11.1986	Lymphatic abscess in abd.	Generalized BCG after vaccination	Yes	
01.1987	Sepsis	Strep. viridians	Yes	
11.1987	Lymphadenitis colli	ND	Yes	
05.1988	Bronchopneumonia bill.	ND		No
11.1988	Abscessus tonsillae dex.	ND		No
02.1989	Abscessus retroauricularis	Candida alb.	Yes	
02.1990	Abscessus axilllae sin	ND		No
06.1990	Abscessus thoracalis sin.	Staph.aureus, Asp.fumigatus	Yes	
12.1990	Bronchopneumonia sin.	ND	Yes	
02.1991	Osteomiellitis costae II sin, Bronchopneumonia sin. Abscessus thoracalis sin.	Asp.sp.	Yes	
10.1991	Cutaneus inf. around cath.	Strep. epidermidis	Yes	
05.1995	Abscessus perianalis	k.- Staph.sp.	Yes	
03.1998	Pneumonia bill.	Candida alb.	Yes	
12.2004	Abscessus hepatis	Actinomyces sp.	Yes	
04.2006	Osteomielitis os.frontalis, Empiema subdurale	Asp. Fumigatus	Yes	
04.2007	Pneumonia, Lymphadenitis	Strep.sp		No

Please choose between different infections:

- Lung infections (pneumonia, bronchitis, pleuritis, …)
- Abscess
  - Subcutaneus
  - Liver
  - Lung
  - Perirectal
  - Brain
  - Lymph node
  - Other - please specify site
- Gastrointestinal tract infections
- Lymphadenitis
- Cutaneus infections
- Osteomielitis
- Ear, nose throat infections (otits, tonsillitis, stomatitis, sinusitis, parotits, rhinitis)
- Meningitis
- Bacteriemia / fungemia
- Other - please specify infection

Date (MM-YYYY)	Chronic complication	Therapy	Hospitalization	
			Yes	No
12.1988	Gingivostomatitis	Local antiseptic		No
10.1989	Gastric outlet obstruction – granuloma pilory	corticosteroids	Yes	
11.1990	Colitis, thickening of gastric wall	Sulfsalazin, cortikosteroids	Yes	
10.1991	Anemia of chr.disease			No
12.1995	Urinary tract obstuction – granuloma ureteris	Op.	Yes	
10.1996	Colitis chronica			No
04.1997	Lymphadenopatia submandibularis			No
10.1998	Loss of pulmonary funtion		Yes	
04.2000	Worsening of pulmonary funtion		Yes	
04.2002	Chronic respiratory insuficiency	Regular th. with O_2	Yes	
01.2003	Short stature, oseoporosis gravis	Ca, Calcitiol, bisfosfonats	Yes	
08.2006	Ileus SI	Op.	Yes	

Please choose between different chronic complication:

- Lymphadenopathy
- Hepato and/or splenomegaly
- Anemia of chronic disease
- Short stature
- Underweight
- Noninfective enteritis / colitis
- Dermatitis
- Gingivitis
- Obstructive lesions (gastric outlet, esophageal outlet, urinary tract) - please specify site
- Pulmonary fibrosis
- Chorioretinitis
- Other – please specify condition

Laboratory:

	Date (DD-MM-YYYY)	SR mm/h	CRP (mg/L)	Leucocytes $x10^9/L$	Thrombocytes $x10^9/L$	Erytrocytes $x10^{12}/L$	Hemoglobin (g/dL)
AO	24.12.1986	110	48	24,8	340	3,5	103
F/U	11.3.1987	3		20,2	286	4,51	108
	7.10.1991	57		11,1	429	4,39	90
	20.5.1996	26		9,4	274	4,77	119
LD			51	9,3	341	5,34	134

Immunologic tests:

	Date	Immunoglobulins (g/dl)				Lymphocyte subpopulation (%)				
	(DD-MM-YYYY)	IgG	IgA	IgM	IgE	T (CD3)	T_h (CD4)	T_c (CD8)	B (CD19)	NK (CD56/CD16)
AO	19.11.1986					70	49	19	19	
F/U	2.10.1990	19,5	1,67	4,25						
LD	…09.1991					79	27	25	32	

	Date DD-MM-YYYY)	NBT	Chemiluminescence	Complement	
				CH50	AH50
AO	…03.1991	0,05	0		
F/U	…09.1991	0,02	0		
LD					

AO: At disease onset; F/U: During follow up (if significant changes); LD: At last determination

Imaging findings:

Date DD-MM-YYYY)	X-ray chest	CT Chest	Pulmonary Function tests
24.7.1990	Chronical pneumopatia with thick pleura on left side;		
..2.1991		Pneumonia chr. of lower left lobe, Athelactasis lobi lingualit, Osteomiellitis coastae II	

Date DD-MM-YYYY)	MRI	U/S Abdomen	Other
9.1.1987		Large spleen, pathological paraaortal lymph nodes;	
3.10.1989		Thickening of distal half of gastric wall and pilorus	
4.12.1990		Hepatoslenomegaly, thick gastric wall	
…12.1995			Sequence scintigraphy of kidneys: signs of hidronephrosis with left uncomplete obst.; possible VUR
17.9.1996		Hepatoslenomegaly, larger left kidney	

Prophylaxis:

Medication	Therapy start (DD-MM-YYYY)	Dose	Interval (… times per…)		Compliance
TMP/SMX	5.5.1988	Various	2x	D	poor
Itrakonazol	8.8.1991	100mg	1x	D	poor
γIFN	…2.1991	50µg/m^2	3x	T	very poor

Compliance: Please indicate, wheter the patient has taken >95% of the drug (**excellent**), >90% (**good**), >75% (**ok**), >50% (**poor**), <50% (**very poor**), no drug (**none**);

Outcome

Chronic condition	Dependant on O_2 therapy
Bone Marrow transplantation	
Diseased	
Other	

Plans for enrollment and data analysis

- 1st phase:
  - To collect clinical data from 30 CGD patients
  - To perform genetic analysis in the genetic laboratory of the University Children's Hospital Ljubljana
    - isolated DNA
    - EDTA blood sample (5 ml)

→ *Genetic analysis available free of charge (Grant of the Slovenian Research Agency)*

Plans for enrollment and data analysis

- 2nd phase:
  - Enrollment of additional patients
  - Proposal for a prospective study
    - Treatment
    - Disease outcome
  - To perform additional protein function studies in collaboration with Dpt. of Biochemistry, University of Ljubljana