

C) Lymphoid Immune System; T-Cell Deficiencies

C-1) The Clinical and Molecular Spectrum of Severe Combined Immunodeficiencies

Luigi D. Notarangelo¹

1. Department of Pediatrics, University of Brescia, Italy

Severe combined immune deficiencies (SCID) represent a heterogeneous group of genetically-determined disorders of lymphoid development that severely compromise T cell development, and to a variable extent B and NK cell development.

While the clinical presentation of SCID is usually characterized by early onset severe respiratory infections, diarrhea and failure to thrive, additional features may also be present, such as erythrodermia or skin rash, and alopecia, particularly in Omenn syndrome or in SCID with maternal T-cell engraftment.

In spite of the rather homogeneous clinical presentation, SCID may associate with distinct immunological phenotypes. In particular, the following forms are well recognized:

- 1) T- B- SCID
- 2) T- B+ SCID (with or without NK cells)
- 3) T (+) SCID

Even more heterogeneous is the molecular spectrum of defects that may cause SCID, with over 30 distinct gene defects identified thus far.

SCID represents truly a medical emergency. Infants with SCID need to be identified as soon as possible, in order to plan for hematopoietic stem cell transplantation (HSCT), that represents the most successful form of treatment for SCID, with an overall cure rate of over 90% in case of HSCT from HLA-identical family donor, and about 70% chance of cure from Matched Unrelated Donors or from partially matched family donors.

Total lymphocyte count and immunophenotyping of circulating lymphocytes are the most powerful diagnostic tools, whereas molecular diagnosis is important for accurate definition of the form of SCID, evaluation of recurrence risk and prenatal diagnosis.

The molecular causes of SCID, although highly heterogeneous, represent defects in one of the following steps along T cell development:

- a) cytokine-mediated signalling and lymphoid progenitors proliferation/differentiation;
- b) expression and signalling through the pre-T cell receptor;
- c) survival of lymphoid progenitors;
- d) positive and negative selection

A correct understanding of the molecular mechanisms that account for SCID has been instrumental to achieve a better view of the mechanisms involved in immune development and function. At the same time, it is essential for development of novel forms of treatment, such as gene therapy.

C-2) Ataxia-Telangiectasia in Iran: Possible Prevention and Therapy

Richard A. Gatti¹ and Mahnoush Babaei¹

1. UCLA School of Medicine, Los Angeles, CA, USA

Background/Objectives: Ataxia-telangiectasia (A-T) is an autosomal recessive disorder caused by mutations in the ATM gene. It is characterized by progressive cerebellar ataxia, oculomotor apraxia, conjunctival telangiectasias, and recurrent sinopulmonary infections secondary to immunodeficiency, cancer susceptibility, and radiosensitivity. The ATM protein is a protein serine/threonine kinase with many downstream targets that involve responses to oxidative stress, cell cycle checkpoints, and DNA repair.

Methods: We analyzed 23 patients from 16 Iranian families for haplotypes, mutations, and their consequences.

Results: We identified 25 (78%) of the expected 32 mutations, on 12 haplotypes. All but two mutations were either truncating or null. Five new mutations were identified. Despite the fact that 75% of patients were homozygous, we failed to identify a founder mutation, suggesting that many undetected ATM mutations exist in Iran. Families came from Tehran, Demavand, Mashhad, Bobol, and Tabriz. These studies establish for the first time a spectrum of ATM mutations for Iran that can be used for diagnosis and potentially for therapy and now allow cancer patients to be screened for these Iranian ATM mutations. In other studies we have found aminoglycosides (AG) can induce readthrough of premature termination (stop) codons (PTCs) in the ATM gene. Only primary PTCs are candidates for this approach; they occur in approximately 28% of A-T patients worldwide. AG induced correction of the

radiosensitive phenotype of A-T cells, indicating that the readthrough ATM protein is functional. High throughput screening is underway to identify the single best readthrough compound, in preparation for animal and clinical studies.

Conclusions: These studies underscore the importance of 1) establishing an accurate molecular diagnosis of A-T, 2) identifying both mutations in each patient, and 3) analyzing the underlying mechanisms of ATM mutations. The principles and drugs being developed for A-T apply to other genetic disorders as well.

C-3) Ataxia-Telangiectasia: Immunological and Clinical Features of 79 Iranian Patients

Mostafa Moin¹, Asghar Aghamohammadi¹, Abolhassan Farhoudi¹, Ali Kouhi¹, Nima Rezaei¹, Zahra Pourpak¹, Masoud Movahedi¹, Mohammad Gharagozlou¹, Maryam Mahmoudi¹, Sanaz Tavassoli¹, Fereshteh Yazdani¹, Saba Arshi¹, Iraj Mohammadzadeh¹, Bahram MirSaeid Ghazi¹, and Anna Isaian¹

1. Immunology, Asthma and Allergy Research Institute, Department of Clinical Immunology of Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran

Background/Objectives: Ataxia-telangiectasia (AT) is an autosomal recessive disease that is caused by mutations of both alleles of the ATM (ataxia-telangiectasia, mutated) gene. AT is an early-onset progressive neurologic disorder associated with a complex phenotype that includes cancer susceptibility, radiosensitivity, and immunodeficiency. In order to determine the clinical and immunological findings of patients with AT, this study was performed.

Methods: The records of 32 patients with AT (17 males and 15 females) with the age range of 3-23 years were reviewed. In order to collect the data on this object, Iranian Primary Immunodeficiency Registry (IPIDR) data were used as the source of information. All the patients were meeting the standard clinical criteria for AT.

Results: Iranian Primary Immunodeficiency Registry has been active since 1997 and 440 cases with a variety of primary immunodeficiency diseases were registered at the end of 2001; among these there were 79 AT patients. In this patient group the total follow up period was 190 patient-years (mean: 3.06 years). The median diagnostic delay in our patient's group was 5 years. At the time of diagnosis, the median serum IgG, IgM and IgA for this group was 1320, 210, and 110 mg/dl, respectively. Level of IgG2 was 75 mg/dl. Alpha-fetoprotein levels were increased in this patient group (mean 120 mg/dl). All of the patients presented with ataxia before 4 years of age. Other neurologic findings were as follows: Speech disorders (31.3%), eye movement problems (12.5%), choreoathetotic movements (6.2%), 4th nerve apraxia (9.4%). Nearly all of these patients had ocular or cutaneous telangiectasia. Most of these patients had infectious problems in their disease course: diarrhea (18.75%), otitis (56.25%), and pneumonia (59.38%). Ten-year survival rate was 30.7% in our patients.

Conclusions: Morbidity and mortality is very high among AT patients because of long period of delay in diagnosis due to limited knowledge of our physicians. Early diagnosis and treatment will result in better outcomes.

C-4) ATM Gene Mutations Detection, Haplotype Analysis, Mt-DNA and D-Loop Variation in Iranian Patients with Ataxia-Telangiectasia

Mahammad Hossein Sanati¹, Behnaz Bayat¹, B. Houshiar¹, M. Houshmand¹, A. Aleyasin¹, Sh. Shariet Panahi¹, M. Montazeri, Anna Isaian², Abolhassan Farhoudi², and Mostafa Moin²

1. National Research Center for Genetic Engineering and Biotechnology, Tehran, Iran

2. Children Medical Center, Tehran University of Medical Sciences, Tehran, Iran

Background/Objectives: Ataxia-Telangiectasia is an inherited autosomal recessive disorder characterized by defect in a number of distinct organ systems. Symptoms include a progressive cerebellar ataxia, telangiectasia, immunodeficiency, chromosomal instability radiation sensitivity and increased incidence of malignancies. The ATM gene of human chromosome 11q22.3 has been identified as the gene responsible for human recessive disease ataxia-telangiectasia (A-T). ATM is encoded in 66 exons and spans 150kb of genomic DNA. In this study 20 families with at least one affected child with clinically suspect for ataxia-telangiectasia were examined and DNA was extracted and amplified by using standard methods.

Methods: Three exons which were hot spot for point mutations in ATM gene were detected by PCR-RELP and SSCP. The polymorphic bands sequenced to detect the possible point mutations. In this manner, mt-DNA was tested by 6 primers for existence of any mitochondrial deletions. We also amplified and sequence the D-loop of these patients by standard sequencing techniques. Likewise four molecular markers: D11S2179, D11S1787, D11S535, D11S1343 were genotyped in A-T families. Those markers were amplified using extracted sequence primers from Gene Bank. The amplified products were separated using denaturing PAGE gels, and the data were analyzed to detect their pattern of inheritance in each family.

Results: We have found three mutations (insertion, substitution) in the examined exons and mtDNA deletions including 2 individuals with 7.5kb deletions, one with 5kb together with a 9.0kb deletion for all. The samples were then sequenced to admit deletion breakpoints.

Conclusions: The results of the D-loop variations related to A-T patients have been discussed in the presentation.

C-5) Identification of P53 Genotype among Iranian Ataxia-Telangiectasia (A-T) Patients

Behnaz Bayat¹, Firouzeh Biramijamal¹, Mohammad Hossein Sanati¹, and Mohammad Mehdi Banoei¹

1. National Institute for Genetic Engineering and Biotechnology (NIGEB), Tehran, Iran

Background/Objectives: Recent studies showed an association between the specific diseases and single nucleotide polymorphisms (SNPs). Ataxia-telangiectasia (A-T) is a cancer-prone and radiation-sensitive syndrome. It is also, a recessive multi-system disorder caused by mutations in the ATM gene at 11q22-q23. The risk of cancer is substantially elevated in A-T patients. It is reported that the ATM/p53 signalling pathway is altered by a very low ATM expression or by the presence of a mutated p53. In the absence of ATM, humans show a primary immunodeficiency that includes low serum antibody titers.

Methods: To investigate the relationship between p53 codon 72 polymorphism and risk for AT, we collected samples from AT patients and healthy population from different region of Iran with different ethnicity groups (Fars, Mazandarani and Turk). The p53 Pro72Arg genotypes were determined by polymerase chain reaction-restriction fragment length polymorphisms (PCR-RFLP) and direct DNA sequencing analysis in 207 healthy controls and 19 AT patients.

Results: Among the patients and healthy subjects with Fars, Mazandarani and Turk ethnicity, the genotype frequency of p53 Pro72Arg were 15.8% and 34.8% for Arg/Arg, 73.7% and 45.9% for Arg/Pro, 10.5% and 19.3% for Pro/Pro, respectively. Significance differences were found for p53 allele distribution among patients and healthy individuals.

Conclusions: Our finding suggested that the frequency of Arg allele is more than healthy Iranian population. This work was supported by NIGEB project number 137 and 197.

C-6) Investigation of NQO1 Genotype Polymorphisms between Iranian Healthy Population and Ataxia-Telangiectasia (A-T) Patients

Mohammad Mehdi Banoei¹, Firouzeh Biramijamal¹, Mohammad Hossein Sanati¹, and Behnaz Bayat¹

1. National Institute for Genetic Engineering and Biotechnology (NIGEB), Tehran, Iran

Background/Objectives: Ataxia –telangectaisa (A-T) is a cancer – prone and radiation sensitive syndrome. The A-T patients are hypersensitive to radiation, free radicals are generated by radiation. The NAD(P)H: quinine oxidoreductase (NQO1) enzyme prevents redox cycling which leads to generation of free radicals. It has been reported that this gene has a single nucleotide polymorphism (SNP) at site of codon 187 (nucleotide 609). A *Pro* to *Ser* substitution at codon 187 of the *NQO1* gene is associated with a loss of NQO1 protein and enzyme activity.

Methods: To investigate the relationship between *NQO1* codon 187 (nucleotide 609) polymorphism and risk for A-T patients. We collected samples from AT patients and healthy population from different region of Iran with different ethnicity groups (Fars, Mazandarani, Turk). The *NQO1* Pro187Ser genotypes were determined by polymerase chain reaction – restriction fragment length polymorphisms (PCR-RFLP) for 206 healthy control and 20 AT patients.

Results: We found only 20 Iranian A-T patients. Among the patients and healthy controls (with Fars, Mazandaran and Turk ethnicities) the genotype frequency of *NQO1* Pro187Ser were 70% and 67% for Pro/Pro, 25% and 28.2% for Pro/Ser, 5% and 4.8% for Ser/Ser, respectively.

Conclusions: No significance differences were found for *NQO1* genotype distribution among patients and healthy individuals. Our finding suggested that *NQO1* genotype does not play an important role in developing Ataxia – telangectaisa.

This work was supported by NIGEB project number 137 and 197.

C-7) The Findings of DiGeorge Syndrome (Chromosome 22q11.2 Deletion Syndrome)

Hulya Kose¹ and Sara Şebnem Kiliç¹

1. Immunology Unit, Department of Pediatrics, Uludag University School of Medicine, Bursa, Turkey

Background/Objectives: DiGeorge anomaly/velocardiofacial syndrome (DG/VCFS) is the most common chromosomal deletion syndrome in humans. DiGeorge syndrome (DGS) is characterized by typical facial features, and conotruncal defects of the heart, parathyroid glands, and thymus. Deletions of chromosome 22q11.2 (Del22q11.2) are the leading cause of DGS. We report on a systematic search by fluorescence in situ hybridization (FISH) for deletions of chromosomes 22q11.2 in patients with a clinical suspicion or diagnosis of DG/VCFS.

Methods: Using fluorescence in situ hybridization (FISH) analysis we studied a series of 43 patients with suspected DG/VCFS. In this study, a total 43 patients were investigated for the presence of a 22q 11 deletion over two years period.

Results: Del22q11.2 was detected in 5 of the 43 patients tested. All had hypocalcemia, 80% had cardiac defects, 40% had dysmorphic facieses, 40 % had immunodeficiency, and 20 % had otolaryngeal abnormalities.

Conclusions: Chromosome 22q11 deletion is a relatively common condition and is readily diagnosed by FISH. We suggest that FISH 22 q11deletion analysis should be performed on patients with hypocalcemia and congenital cardiac malformations. It has permitted us guidelines to facilitate early diagnosis.

C-8) Presentation of Seven Patients with Idiopathic CD4 T Lymphocytopenia

Mohammad Gharagozlou¹, Marzieh Heidarzadeh¹, Mahboubeh Mansouri¹, and Anna Isaian¹

1. Immunology, Asthma and Allergy Research Institute, Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran

Background/Objectives: Idiopathic CD4 T Lymphocytopenia (ICL) is an unusual Immunodefect in which there is an unexplained deficit of CD4+ T cell leading to fungal, parasitic infection, disseminated tuberculosis, human papillomavirus, hepatitis C and CMV infection. In addition, some of them are in asymptomatic state. They are also prone to neoplastic and autoimmune disorders.

Methods: We introduce 7 cases of ICL with heterogenous clinical manifestation, in different range of ages.

Results: The range age of these patients were between 4 and 25 years. Clinical symptoms were related to skin include eczema, recalcitrant wart, pustular eruption, abscess formation, and psoriasis. Otitis media, sinusitis, bronchiectasia, pneumonia, gastrointestinal manifestation have constitute the other clinical features. Laboratory findings was included: normal to elevated of all Ig classes, variable response in LTT result, CD4+ T cell count less than 20% total T cell; There was not any evidence of HIV infection. Moreover the results of other Immunologic studies were normal.

Conclusions: Despite high prevalence of ICL among intravenous drug user and hemophiliacs any causative infection for CD4+ Tcell declining was not found in our patients. There were differences in our studies: In all of our cases, the disease has begun in childhood and in most of them Immunoglobulins especially IgA and IgE levels were elevated. All of our patientes had shown wartous lesion in different ages. There is no difinit treatment till now expect propylaxy and treatment of infection. Recently, most of the patients had benefits from IL-2 and bone marrow transplantation therapy.

C-9) Introducing Severe Combined Immunodeficiency Patients with Different Phenotype

Marzieh Heidarzadeh¹, Abolhassan Farhoudi¹, Zahra Pourpak¹, and Anahita Azimdoost¹

1. Immunology, Asthma and Allergy Research Institute, Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran

Background/Objectives: The severe combined immunodeficiency disease is disorders of host defense in which there is significant impairment of both humoral and cellular immune function. The overall frequency is estimated to 1 in 75000 – 100.000 births. The clinical presentation is characterized by early onset of infections especially caused by oportunist organisms, mainly of the respiratory tract and gut, oral candidiasis , persistent diarrhea with growth impairment, infection after live-virus vaccines on bacile galmette – gurein vaccination, GVHD, increased incidence of malignancy. Based on the results of flowcytometry, the phenotype of the immunodeficiency can be categorized as T cell positive or negative, B cell positive or negative and NK cell positive or negative

Case report: We introduced the phenotype of 21 SCID cases from 1987 to 2004 in Children's Medical Center of Iran according to their flowcytometry results (11 male, 10 female). The most common clinical manifestation of this patients were, early onset symptom , oral candidiasis , chronic diarrhea, FTT and fatal infections after live – vaccine

18 cases of this patient had died by one year ago. BMT was done for one of the cases. Two cases with distinct clinical symptoms have been considered, omenn syndrome. The Base on flowcytometry results, the phenotype of this patients was T⁺B⁻N⁻ (3 cases), T⁺B⁻N⁺ (6 cases) T⁺B⁺N⁺ (9 cases) and T⁺B⁺N⁻ (4 cases).

Conclusions: These phenotypes can more easily be associated with a more limited number of genetic defects and the farther characterization of the child immunodeficiency can be delineated accordingly. Previous evaluations were revealed that approximately 70% of human SCID cases were T⁻B⁺ and 20% to 30% was T⁻B⁻. Our results are compatible with these results.

C-10) Does Really This Well Developed /Well-Nourished Infant have SCID?

Sara Kashef¹, Reza Amin¹, Mojgan Kiani¹, and Soheila Aleyasin¹

1. Department of Immunology and Allergy, Nemazi Hospital, Shiraz University of Medical Sciences, Shiraz, Iran

Background/Objectives: Severe combined immune deficiency (SCID) is a syndrome of diverse genetic causes that lead to death in infancy or childhood without bone marrow transplantation. Patients with SCID often have recurrent or chronic severe infections and failure to thrive. Growth is normal initially but extreme wasting occurs after infections begin. The most leading cause of death is persistent opportunistic infections: *Candida albicans*, *P. carini*, CMV, EBV, and *Bacillus Camett-Guerin* (BCG). In the present article, we describe a 3-month -old, well looking female infant with SCID disorder who came with history of prolonged fever and skin rash, long before admission.

Case report: She had been injected with BCG vaccine few days after birth. Her family history revealed early infancy death in her brother. Her immunologic investigation also revealed severe lymphopenia (combined B and T cells). She was found to have disseminated BCG infection with a good response to Isoniazid and Rifampin.

Conclusions: Although she continued to live for next seven months, she died because of complications of an opportunistic pneumonia.

C-11) Digorge Syndrome: Case Report

Barbara Schofield-Suleiman¹ and Vicki-Jo Deutsch¹

1. Terence Cardinal Cooke Health Care Center, USA

Background/Objectives: DiGeorge syndrome consists of a pattern of malformations which invariably include defects of the development of the thymus, parathymus and great vessels. Abnormalities may include: 1) Thymus-hypoplasia to aplasia with deficit of cellular immunity allowing for severe infections. 2) Parathymus-hypoplasia to absence allowing for severe hypocalcaemia and seizures in early infancy. 3) Cardiovascular-aortic trunk anomalies including R aortic arch, interrupted aorta, conotruncal anomalies, patent ductus arteriosus and tetralogy of Fallot. 4) Facial-tendency to hypertelorism, short philtrum, downslanting palpebral fissures, ear anomalies. Occasional anomalies: mental deficiency mild to moderate, esophageal atresia, choanal atresia, imperforate anus, diaphragmatic hernia. Etiology: micro deletion of the chromosome 22 accounts for more than 90% of the cases.i.e.22q11.21-23 being the most frequent. Exposure to alcohol and other toxins such as retinoids in the intrauterine stage can also result in similar phenotypic syndromes. Path physiology: interruption of the normal development of the 3rd to 4th pharyngeal pouch structures near the 8th week of gestation. Frequency: 1:4000 in USA. Mortality/Morbidity: congenital heart defect is the main cause of mortality (8% in report of Ryan et al reviewing 558 patients), most deaths occurring within 6 months of birth. Infections due to severe immune deficiency are the second most common cause of mortality.

Case report: D.M. is a 4 year old boy admitted to our facility 3/02 for rehabilitation therapy and management of his medical problems. He was born on 9/26/00 at 38 weeks GA via NSVD to a 24 year old mother G3 P1 F1 A1 L1, Apgars 5 at one minute, 2 at five minutes and 4 at 10 minutes. B.Wt 2.85 kg (10%), L 47cm (10%), HC 32 cm (5%). He was intubated in the delivery room and transferred to the NICU on a conventional ventilator and changed to a High flow ventilator. He continued to deteriorate and was transferred to a tertiary care hospital where his care was complex. On admission he was placed on ECMO 9/27/00-10/6/00. On extubation he developed stridor. Laryngoscopy revealed bilateral vocal cord paralysis. High KV films revealed subglottic stenosis. A tracheostomy was placed 11/01/00. An echocardiogram revealed a VSD with bi-directional shunting and normal ventricular function. Neurological exam at that time described an increase in axial and extremity tone with clonus bilaterally. An MRI of the brainstem, a head and renal US were all normal. Ophthalmology exam was normal. Because of poor nipple and GER, demonstrated by a cine esophagram, a GT was placed and a fundoplication done on 12/27/00. A karyotype was positive for a 22q11 deletion. ENT performed endoscopy on 3/02 which showed narrow choanae bilaterally L>R. Vocal cord movement was observed. Audiology demonstrated normal hearing. An elective cardiac catheterization was done 4/10/01 demonstrating: Subpulmonic VSD with L to R shunting; pulmonary hypertension reactive to oxygen; Normal pulmonary vascular resistance on 100% oxygen. He had significant developmental delay.

After 6/01 he was weaned off the ventilator. A modified barium swallow performed at that time demonstrated no aspiration and only a slight delay swallowing. Oral feeds were started. Corrective open heart surgery took place 6/11/01. Post op course was rocky and there was difficulty weaning him off the ventilator. On 8/13/01 an EKG was normal, an echocardiogram showed mild pulmonary insufficiency and global ventricular performance within normal limits. D.M. was admitted to Terence Cardinal Cooke Health Care Center on 3/5/02 at age 1 year 6 months with the following diagnoses: DiGeorge syndrome with a 22q11 deletion; GERD S/P GT; S/P trach on shiley ped 4.0 trach; S/P cardiac surgery; Developmental delay. D.M. has done remarkably well since admission. He has had no significant infections, despite the fact that his trach serves as a potential portal of entry for infection. He does have intermittent skin infections consistent with tinea corporis which always respond well to nystatin topical therapy. Developmentally he continues to gain milestones, being verbally communicative, with increasing attention span and able to identify objects in books. He sings his favourite nursery songs. He is potty trained. His diet is entirely p.o. with a chopped food diet. His calcium has remained normal and he has had no seizures. Phenotypically he has no significant dysmorphic features. He is followed by cardiology, immunology and ENT clinics: Cardiology 4/04 –EKG normal; Echo no residual VSD; Immunology 9/04 – immunological status continues to show significant T cell; Lymphopenia. He had a good response to his MMR booster in 8/04 suggesting that he does not have a significant functional cellular deficiency at this time. Labs: WBC 7.6, Hgb 12.3, Hct 35.2, MCV 79.9, Plt 282, Neut 57.4%, Lymph 27.2%, Mon 6.9%, Eos 8.1%, Bas 0.4%. Lymphocyte screen revealed normal numbers of NK cells 13% (275 cells/cu mm) and B cells 58% (1199 cells /cu mm). Total T cells were 21% (436 cells /cu mm), Helper cells 11% (236 cells /cu mm), Suppressor cells 8% (163 cells /cu mm), and Helper/Suppressor ratio 1.4. He had protective titers to measles, mumps and rubella post MMR booster. TSH was normal at 1.94 uIU/ml ENT 10/04 - a bronchoscopy is being planned in order to evaluate the possibility of decannulation.

Conclusions: D.M. has a chromosome 22q11 deletion known as Di George Syndrome. CATCH 22 Syndrome (Cardiac, Abnormal facies, Thymic hypoplasia, Cleft palate, and Hypocalcemia) includes the broad spectrum of conditions associated with 22q11.2 deletions. The majority of patients with 22q11.2 deletion do not have an affected parent; therefore the change in their chromosome 22 is a new mutation. An individual with that mutation has a 50% chance of passing on the chromosome with the deletion to his or her offspring. D.M. demonstrates a partial degree of immunodeficiency with significant T cell lymphopenia, normal Natural Killer cells and normal B cells. He has been notably free of infection except for recurrent episodes of tinea corporis which respond readily to topical therapy. The cardiac defect of subglottic VSD with L to R shunting was corrected successfully, and the pulmonary hypertension resolved. No hypocalcaemia was demonstrated. There is no cleft palate nor are there dysmorphic features. With his progressive gain of appropriate milestones in development, his normal weight gain on po feeds only and the possibility of decannulation, the prognosis for D.M. is excellent. He receives bacterial endocarditis prophylaxis for dental procedures. He will continue to be monitored by immunology every 6 months and by cardiology annually.

C-12) Is the HLA II Deficiency a Maghreb PID?

Ahmad Aziz Bousfiha¹, Fatima Ailal¹, Hamid Naaman², Hassane Fellah², Ouafae Maataoui², Ibrahim Farouqi², and Abderrahmane Abid²

1. *Unité d'Immunologie Clinique, Hôpital d'Enfants, Centre Hospitalo-Universitaire IBN ROCHD, CHU AVERROES, Casablanca, Morocco*

2. *Laboratoire d'Immunologie, Hôpital d'Enfants, Centre Hospitalo-Universitaire IBN ROCHD, CHU AVERROES, Casablanca, Morocco*

Background/Objectives: Major histocompatibility complex class II deficiency is an autosomal recessive combined immunodeficiency. About one hundred cases have been reported worldwide. It seems to be particular to the Maghreb region because about 70 % of all known patients, notably the B group of complementation was from this region. The disease is characterized by a genetic heterogeneity with at least four complementation groups. Although, the clinical phenotype is comparable enough, dominated by denutrition, protracted diarrhea and interstitial pneumonia. Cholangitis are so specific of this combined immunodeficiency.

Methods: Our survey carried on 8 cases collected between 1997 and 2004.

Results: These 8 cases represent 6 % of our PID and 14% of our combined immunodeficiencies. In the other countries this proportion is between 0.2 to 2% of PID and 1.5 to 4 % of the combine immunodeficiencies. In Tunisia, these proportions are 6% and 36%. A founder RFXANK mutation (**752 delG-25**) of the disease has been finding in this population.

Conclusions: Our set was characterized by the severity of the clinical phenotype, especially by the therapeutic means insufficiency. A considerable effort should be achieved in order to improve reception structures, tools of diagnosis and the hold in charge, notably bone marrow transplantation development.

C-13) Role of ICAM- 1 Deficiency in Patient with Familial Chronic Nail Candidiasis

Najibeh Asl Rahnemai Akbari¹, Mohammad Adibpour¹, Mehry Rajaii¹, and Iran Nokhahi¹

1. Department of Immunology- Parasitology, Medical School, Tabriz University of Medical Sciences, Tabriz, Iran

Background/Objectives: Chronic mucocutaneous candidiasis is primary immune deficiency presenting as inability to clear fungal infections and consequently as persisting and recurring infections of the skin, nail, mucous membranes with yeasts, mostly *Candida albicans*. Familial occurrence of CMC was originally reported by Wells et al, who described both males and females affected and consanguinity in a number of their pedigrees. Investigators have described a distinct form of familial chronic nail candidiasis (FCNC), characterized by early onset infections caused by different species of *Candida*, restricted to the nails of the hands and feet, associated with low serum concentration of intercellular adhesion molecule I (ICAM-1).

Methods: Some of patients that consanguinity in number of their pedigrees, with nail dystrophy, hyperkeratosis and dark, thick nails were selected, based on clinical and anamnestic records. The CMC diagnosis was currently performed through the mycological analysis of nail specimens obtained by cutting and scarping the lesion sites; serum ICAM-1 levels were assayed on the affected and unaffected family members, and controls, sex and age matched, using anti-ICAM-1 human antibody.

Results: All patients were infected by different kinds of the genus *Candida*. The mean ICAM-1 level and concentration in the affected subjects was 63.29 (SD 14.36) ng/ml, compared to 108.31 (SD 13.57) ng/ml in the unaffected relatives and 133.24 (SD 18.36) ng/ml in the controls (ANOVA test, $p < 0.05$).

Conclusions: Intercellular adhesion molecule-1 (ICAM-1 or CD54) is a glycoprotein membrane and a member of the immunoglobulin super family which plays a central role in cell mediated response and is a ligand for leukocyte function associated antigen-1 (LFA-1). There is a clear clinical concordance between ICAM-1 serum levels and nail dystrophy. However, the pathogenesis of the nail lesions is unclear; the relationship with the reduced ICAM-1 expression awaits clarification.

C-14) Immunological Conditions of Children with Disseminated BCG Infection in Children's Hospital of Tabriz

Mahnaz Sadeghi Shabestari¹, Reza Baradaran¹

1. Division of Immunology and Allergy, Children Hospital, Tabriz University of Medical Sciences, Tabriz, Iran

Background/Objectives: BCG, an alive attenuated vaccine, protects children from millitary tuberculosis and tuberculosis meningitis by stimulating cell mediated immunity. Adverse reactions of BCG are rare (0-23.8%). Lymphadenitis and osteitis is the most common complications of this vaccine. But in the rare instances BCG vaccine can cause disseminated infection, the most serious complication of vaccine. According to references this rare reaction occurs in 1 per 1000000 cases but in our country it seems is more common. Four from of immunodeficiency were known as underlying condition: 1-Severe combined immunodeficiency (SCID). 2-Cell mediated immunodeficiency (CMID.) 3-Acquired immunodeficiency syndromes (AIDS) 4-Chronic granulomatous disease (CGD). Disseminated infection is lethal in 50-71% of instances and in 86% of cases, temporary or permanent immunodeficiency has been detected.

Methods: Infants who admitted in hospital because of chronic lymphadenitis after BCG vaccinations were assessed completely according to clinical, radiological, and laboratory criteria.

Results: In one year, 7 cases of disseminated BCG infection were found in children's hospital. All of them were younger than 7 month of age, and half of them were male. Most common signs and symptoms: -Fever and Anemia (all of causes), thrush, refractory diarrhea, hepatosplenomegaly, bone lesion (osteitis and osteolytic); -Chronic fistulized lymphadenitis, ulcer at the site of injection, bilateral lymphadenopathy. Smear and culture for calmette-guerin bacillus were positive in gastric lavage of some patients. Parents was relative in 1/3 of patients, in one case, there was a history of similar disease in his brother. All of them had SCID and response to therapy was poor leading to head in 5 cases.

Conclusions: Disseminated BCG infection occurs mainly in immunodeficient patients and has a high mortality rate. On the other hand, in children with inherited immunodeficiency caused by altered function or absence of T lymphocytes, vaccination with BCG is unfortunately connected with extreme risk of systemic life-threatening infection. So, it is possible that with early diagnosis of high risk groups, we can reduce the mortality and morbidity rate of this serious complication.

C-15) A Clinical Association between Chronic Mucocutaneous Candidiasis and Class I Histiocytosis: A Case Report

Mahboubeh Mansouri¹, Setareh Mamishi¹, Mehrzad Mehdizadeh¹, Fatemeh Mahjoub¹, and Abolhassan Farhoudi¹
I. Immunology, Asthma and Allergy Research Institute, Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran

Background/Objectives: Chronic mucocutaneous candidiasis (CMC) refers to a group of immunodeficiencies characterized by persistent or recurrent infections of the skin, nail and mucus membranes caused by organism of the genus candida. Seven types of clinical syndromes in CMC are reported by the authorities. CMC can be localized to oral cavity, familial, localized to mucus membranes and skin, or may be associated with polyendocrinopathy, thymoma, hyper IgE and keratitis.

Childhood histiocytosis encompasses a group of diverse disorders that have in common a primary event, the accumulation and infiltration of monocytes, macrophages and dendritic cells in affected tissues, which are classified based on histiopathologic findings as class I, class II and III. Class I or langerhans cell histiocytosis (LCH) has an extremely variable presentation ranging from mild to life threatening.

Case report: Here we introduce an infant boy aged 1 year, with no similar history in the family, presented with scaly erythematous patches on scalp and face, purulent discharge from ear and eyes, deep skin fissures in intertriginous area, hepatomegaly, oral and genital candidiasis and dystrophic changes in finger nails compatible with candida infection. Immunoglobulin G and E and IgG subclasses levels were normal but IgA and IgM levels were very elevated, flowcytometric evaluation (CD3, CD4, CD8, CD19, HLA DR) was not suggestive. HIV serology was negative. Skin test with candida showed no reaction. One lytic bone lesion was seen in skull x ray. Bone marrow aspiration was normal. Skin biopsy was diagnostic for Langerhans cell histiocytosis. Patient received amphotericin B intravenously. Oral, genital candidiasis and deep skin fissures were greatly improved. He is receiving chemotherapy and his general condition is good.

Conclusions: Normal langerhans cell are APCs and activators of T lymphocyte. many immunological deficit such as decreased proliferative response to DHA, ConA, PWM and tetanus antigen or decrease in both CD4 and CD8 and also in CD4+ / CD45RO and increase in CD4+/CD45RA+ are reported in LCH, but anergy to candida antigen is not a usual finding and association of these two different clinical conditions is rare and not reported previously. Should we consider CMC, as a consequence of immunological abnormalities in LCH, or it would be possible that LCH accompany CMC, like other clinical syndromes which associate CMC.