ESID Newsletter

Contents

The ESID Newsletter is made for the members of ESID – the European Society for Immuno Deficiencies.

It is published under the responsibility of the ESID Board, and at this moment it is edited by Esther de Vries (editor in chief), Lucia Bianchi, Ales Janda, Gustavo Lazo, Nima Rezaei, and Crina Samarghitean.

Any ESID member who is interested in publishing his or her views, research, new ideas or other material in the ESID Newsletter is cordially invited to submit copy to the Editor. Suitability for publication is assessed by the Editor in consultation with the other members of the ESID Board.

Editorial address:
Dr. Esther de Vries, pediatric immunologist, Jeroen Bosch Hospital loc GZG, P.O. Box 90153, 5200 ME 's-Hertogen bosch, the Netherlands, tel. +31-73-6992965, fax +31-73-6992948.

Please only use my *new email address*: esid@ estherdevries.nl

Front page: Carnaval in `s-Hertogenbosch, the city of our next biennial meeitng..

Dear ESID members,

The ESID biennial meeting is getting near, and I hope to see all of you in the beautiful city of `s-Hertogenbosch in October! Do visit the meeting website at www.esid2008.org and register for the meeting in time for the deadline for early registration. This will save you a lot of money… We are also eagerly awaiting your abstract submissions through the website.

Because I have been very busy with the organisation of the meeting, I haven't had as much time as usual to spare for the ESID Newsletter. That is why this is a combined issue: 2007-4 & 2008-1 …

Please note that it is time to pay your ESID membership fee 2008-2009. It will entitle you to the reduced meeting registration fee, and to attend the members-only gala dinner.

You will find lots of interesting information in this issue on all kinds of ESID activities. Do note the call for candidates for offices within ESID, the call for collaboration from Klaus Warnatz, and the intriguing interview with prof. Aziz Bousfiha from Morocco in the PID-care in development session.

Best wishes to all of you,

Esther DE VRIES

ESID is the European Society for Immunodeficiencies. It was formed in 1994. The forerunner of ESID, the informal European Group for Immunodeficiencies (EGID) was established in 1983. The aims of this society are, among others, to facilitate the exchange of ideas and information among physicians, scientists and other investigators who are concerned with immunodeficiencies and to promote the research on these diseases. Anyone who is interested in primary immunodeficiency diseases can become a member of ESID. Registration is possible online at www.esid.org/members.php.

Within ESID, seven Working Parties are actively engaged in coordinating the member's joined efforts in patient care and research in primary immunodeficiency diseases: Stem cell transplantation and gene therapy (chair: Mario Abinun), Registries (chair: Gerhard Kindle), Clinical (chair: Bobby Gaspar), Genetics (chair: Naomi Taylor), Education (chair: Andrew Cant), PID-care in development (chair: Laszlo Marodi), and ESID *juniors* (chair: Eleonora Gambineri). Anyone who is interested in participating in one or more of these Working Parties is invited to do so. Please contact the chairman of the relevant Working Party (contact information is available at www.esid.org /board.php).

In 1994, a main registry of patients with various forms of immunodeficiency in Europe was established. Altogether, data from some 10,000 patients from 26 countries was compiled until 2002. However, given various shortcomings of this registry, ESID decided to develop a new state-of-the-art database for primary immunodeficiencies. This online registry was launched in 2004 and contains subregistries for more than 150 primary immunodeficiencies. It combines both clinical and laboratory data of PID patients and offers the possibility to document genetic data as well. Up to date, more than 2,000 patients have been registered in that database. Information, database statistics and a demo version of the registry can be found at www.esid.org/registry.php, or send an email to registry@esid.org.

The new ESID Online Registry is connected to the mutation databases (IDbases) in Tampere, Finland. These were created since 1995, when the first locus-specific immunodeficiency mutation database accessible through the internet was established (BTKbase for X-linked agammaglobulinemia). Since then, more than 100 additional locus-specific databases have been established. Information is available at http://bioinf.uta.fi.

ESID organizes a biennial congress to facilitate international contact between primary immunodeficiency specialists. The last congress was organised in 2006 in Budapest, Hungary , and the next one will be October 16-19 in `s-Hertogenbosch, The Netherlands, in 2008. Information is available at www.esid2008.org.

= ESID Information =

Secretarial report

ESID business in 2008 will be dominated by our biennial meeting in s'Hertogenbosch. Esther de Vries, the meeting's president and the scientific committee are currently working together with the ESID board on the second announcement, due to be published in February 2008.

Anybody who will need extra rooms in s'Hertogenbosch for a satellite symposium shall please contact Esther directly via Email.

The Educational Day shall be free for all ESID/INGID/IPOPI meeting participants. Seating restrictions will apply to implement a new interactive format: ESID Juniors will sit in the front and participate; seniors will be asked to sit in the back and listen.
There shall be a separate abstract category for INGID and one for ESIDjuniors

Another very important topic in 2008 will be the notarial deed for the legal act. This is planned for April 2008 by Esther.
The ESID board is busy preparing a new Constitution draft as well. This will be put forward to the GA in 's-Hertogenbosch where we still have to vote on this final version.

The upcoming elections for ESID officers will be possible by online voting only. Successors for Mario (SCT and BMT working party) and Bobby (Clinical Working Party) and Esther, the ESID treasurer, have to be identified. Anybody who is interested in these posts shall please contact any of the Board members, and send there application to Esther de Vries and Bodo Grimbacher for publication on the web and in the ESID Newsletter.

The ESID board decided to try to team up with an international congress organization for the ESID meetings following the one in Istanbul in 2010. Four agencies were contacted, and the board asked the secretary to proceed with his contacts to KENES to come to a proposal for their long term involvement as a congress organizer and as the managing partner for the society after approval by the GA.

There is concern that the ESID website is not sufficiently used / promoted, especially since nobody responded to the job advertisements placed there during the last 12 months. The ESID forum is not well used; also there is almost no traffic to the ESID research protocols. It was suggested that in order to increase the traffic to the ESID website, the secretary may circulate emails to all ESID members regarding new developments within ESID or important to any ESID business or any interest of ESID. These notes can be submitted to the secretary for dissemination by any ESID member. When a new posting is made on the forum, email alerts may be sent to al ESID members, not only the ones who have signed up for the forum.

The ESID newsletter. Esther was asked by the board to continue her work as the Chief Editor of the ESID newsletter until 2010, despite her resignation as treasurer in Oct. 2008. As the 2008 ESID meeting president, she will be part of the ESID board until 2010. This might also ease the transition to a new treasurer for ESID from 2008 onwards.

On the UKPIN website (www.ukpin.org.uk) there is available an online version of the ESID diagnostic protocols.

Klaus Warnatz from Freiburg suggested an ESID lymphocyte phenotyping protocol which has been endorsed by the ESID board. You will find more information on this new ESID project in this newsletter, as well as a summary of all current ESID studies as compiled by Gerhard Kindle, head of the ESID registry.

I was asked to evaluate the potential benefits and obligations when signing up as a partner organization with CIS/FOCIS and / or EFIS. Any input here will be greatly appreciated.

Bodo GRIMBACHER

Treasurer's report

Dear ESID members, it is time to pay your membership fee for 2008-2009. The amount you have to pay is the same as for 2006-2007. If you haven't yet paid 2006-2007, you will have to do this first!

It will not be possible to register as a member for the `s-Hertogenbosch meeting if your membership fee has not been paid in time. The congress organisation will check this before sending you your invoice, and will charge the non-members registration fee if you haven't paid your ESID membership fee 2008-2009. You can correct that, but if you do that after the early registration deadline, you will be charged the late registration fee for the meeting, albeit the fee for members.

So, don't forget to pay in time, and join us in October in `s-Hertogenbosch !!

Esther DE VRIES

News & Views

ESID Elections for Board members are on the way — candidates needed !

According to our present Constitution, all candidates who are elected as officers of ESID are elected for a term of 2 years, once renewable. Only the treasurer can be elected for a total of 8 years. The president-elect is elected 2 years before his/her office starts, and biennial meeting presidents are elected 4 years before the meeting, and remain part of the board for 2 years thereafter. ESID Board members have to be ESID members, and the president has to be an ESID member of two years standing.

The following people can be re-elected for their office for another term of 2 years:
* President: Jean-Laurent Casanova
* Secretary: Bodo Grimbacher
* WP Registries: Gerhard Kindle
* WP Genetics: Naomi Taylor
* WP Education: Andrew Cant
* WP PID-care in development: Laszlo Marodi
* WP ESID*juniors*: Eleonora Gambineri

It is possible for alternative candidates to put themselves up for election.

The following people cannot be re-elected for their present office anymore:
* Treasurer: Esther de Vries
* WP SCT&GT: Mario Abinun
* WP Clinical: Bobby Gaspar

The following offices have to be filled:
* President-elect
* Meeting president 2012

Candidates are needed, and all ESID members are heartily encouraged to ask information about these offices from current or previous Board members and to put themselves up for election !

The ESID Board

Alain Fischer received the 2007 Debrecen Award for Molecular Medicine in December last year

Interview with Professor Alain Fischer, prize winner of the Debrecen Award for Molecular Medicine 2007:

What does this award mean for you? How do you appreciate that this year you received the Debrecen Award for Molecular Medicine?

Well I am very honoured it is a prestigious award, my predecessors are very famous scientists: geneticists, immunologists, molecular biologists. So I feel very proud to be together with them .This is also actually a recognition of the contribution of many scientists in Europe and worldwide to the field of primary immunodeficiency diseases .

Have you ever been to Debrecen? What is your impression of the University of Debrecen?

I am very glad to be here. It seems to me that this university is very dynamic, is trying to push the walls, and become very active in teaching and research in Europe.
This is my first visit to Debrecen. I know very well Professor László Maródi, first time we met was about 20 years ago. We work on the same field, he is very active clinician scientist, and he has done a lot not only for Debrecen, but for all Eastern Europe. He has been extremely efficient in promoting a network of doctors from several countries in Eastern Europe thus ensuring better diagnosis, treatment of patients with primary immunodeficiencies and also fostering clinical research projects If everyone is like him here, it is great. I also met the Dean and the Rector it seems to me that there are very active in driving new projects and it looks good to me.

What do you think, what were your most important publications?

If you want me to ask about one, it is difficult. I like to mention identifying the cause of genetic diseases leading to defective Immunoglobulin class switch recombination (CSR). This process is very important in the maturation of antibody responses. In the early 90s,G. de Saint Basile (among others) identified CD40 ligand deficiency and in 2000, A. Durandy found activation-induced cytidine deaminase (AID) deficiency. These were two crucial steps in the understanding of the mechanism involved in the generation of CSR and also of somatic hypermutations of the variable segments of immunoglobulin genes. These results illustrate how the study of diseases can enlighten physiology!

Maybe another one is gene therapy of the X linked SCID. Together with M Cavazzana-calvo,we were the first to treat successfully an immunodeficiency by gene transfer.

Do you think, it is possible to modify gene therapy without oncogenic risk?

We hope so very much. There are two reasons for oncogenesis after gene therapy.
First, oncogenesis that occured in 4 of 20 patients with X-linked SCID treated by gene transfer,was related to the retroviral vector utilized, but also possibly to the disease itself, because this adverse effect has not been observed in in other diseases including the successful gene therapy of adenosine deaminase deficiency. There might thus be a specific component related to that disease.
Second, it is possible to modify the vector used in the X-SCID gene therapy trialin order to reduce the risk of oncogenesis. The mechanism involved relates to the transactivating capacity of a viral element – the so called LTR. Once integrated into the genome, the virus can thus trigger aberrant

expression of a protooncogene close to which it is located,as observed with the LMO-2 gene. By deleting the enhancer element of the LTR in the vector, the oncogenic risk is likely to be much reduced. This has not yet been proven in clinical trials, but they are underway in collaboration with collegues from Germany, UK and the US.

When will you think gene therapy become common in the daily routine of the clinical practice?

The number of diseases where gene therapy can be used is today very limited. Clear success has been reached only in two very rare severe combined immunodeficience diseases: X-linked SCID and adenosine deaminase deficiency because a clearcut selective advantage was provided to transduced cells by expression of the 'therapeutic' gene. There are a few preliminary results suggesting possible extension. For example, Italian collegues have been able to correct a genetic defect of the skin leading to a dreadful disease, i.e. one form of epidermolysis bullosa. Skin stem cells were ex vivo transduced differentiated, and put back as grafts into the skin. After one year, these skin sections were normal. Although limited to one patient and preliminary, it is a spectacular achievement raising hope for further development.

Advances in gene therapy are likely to combine advances in vector design and a better knowledge of diseases to be treated. Primary immunodeficiency diseases are likely to be major targets for that approach because hematopoietic stem cells are accessible and pathophysiolgy of these diseases is better and better understood.

Why did you choose this field: paediatric immunology?

That is a good question. By chance, just by chance. When I was a medical student, like you, I went to a ward and saw a few patients with immunodeficiency diseases. That was in the early 1970s. In that time one knew very little about immunodeficiencies, so patients were not doing well. I was struck by the way these patients were taking care. And also I had the feeling, that scientifically speaking it should be an extremely challenging field providing that we were able to understand better these kinds of diseases. So it was by chance, and I go on with it since then.

You mentioned in your Hungarian preface of your lecture, that your father is from Hungary. Can you tell us a few words about your family?

My father was born in Poland, in the time when it was part of the Empire of Austria-Hungary, but his family moved to Budapest in 1918, when he was 9 years old. So as a child and as a young adult he lived in Budapest. But actually he studied in Vienna where he was living in the same street as Sigmund Freud was. After his studies he went back to Budapest, and he established a small company producing pressurized water bottles. As a Jew he considered that the situation was becoming very critical and it was very risky after the Munich Agreements, when the Czech Republic was disappeared. He felt that things were going wrong and that this was not going to be the place to stay. He considered that France would be the place to stay – unfortunately France was not either a good place to stay. He survived the war in France, and then he met my mother.

Have you got a special message to the medical students of the University of Debrecen?

Yes, that is the most important question. I think you should be passionate with your studies and after that with your work. Medicine is fantastic and there are many opportunities and many things that can

be done in this field. One of them is research, not the only one of course, but for those of you who are interested, just go ahead, learn a lot, as much as you can about science and try to apply to medicine, this will make progress in medicine. And of course you as medical students of the world are the future of medicine. Innovative options are in how to treat better and to take better care of patients. There are many things to be done, genetics is one, but there are many others: neuroscience, public health, and epidemiology, whatever everything is fantastic just go deep into one given field. Go abroad, watch how it works in another countries, universities, hospitals or laboratories, meet people, learn different techniques, and know new methods. Be enthusiastic.

Edit Posta and Levente Lánczi,
3rd and 5th year medical students.
University of Debrecen Medical
and Health Science Center

After the ceremony, Alain Fischer and his wife visited the Debrecen Jeffrey Model PID Reference Center at the Department of Infectious and Pediatric Immunology. Anne Marie Fischer (L), Alain Fischer (M), László Maródi (R).

The 20th J-PROJECT Meeting was held in Ohrid, Macedonia, 20-21 September, 2007, hosted by Kristina Mironska.

The meeting was held in the Hotel Metropol, Ohrid. The main topic was genetic diagnostics and complex management of patients with primary immunodeficiencies in East Europe. The following speakers were present: Bernatowska E, diagnostic and therapeutic guidelines for PID; Marodi L, Molecular genetic analysis of Hungarian patients with the hyper-IgM syndrome; Sulcebe G, PID diagnosis in Albania; Spirovski M, Laboratory diagnostics of PID in Macedonia; Baltadjieva D, Flow cytometric assays for in the diagnostics of PID; Sukarova-Angelovska E, Early diagnosis of DiGeorge syndrome; Peova S, Mironska K, Kareva L, Stavrić K, Macedonian report of PID in children; Pasic S, SCID in Serbia: clinical presentation, diagnosis and outcome; Pac M, the clinical features of patients with X-linked agammaglobulinemia; Kareva L, Peova S, Mironska K, Stavric K, Joint disease in children with XLA; Petrova G, Perenovska P, Job syndrome; Mironska K, Peova S, Kareva L, Stavric K, Wiskott-Aldrich syndrome in female patient; Kurenko-Deptuch M, Clinical and genetical aspects of chronic granulomatous disease in patients of the dept of Immunology, CNHI, Warsaw; Stavric K, Peova S, Kareva L, Mironska K, Autoinflammatory disorders; Bataneant M. et al, PNP deficiency

SUMMARY AND CONCLUSIONS:

In September 2007, for the second time in Macedonia, a meeting of the participants in the J-Project for PID was held. The idea this meeting to be organised as part of the Fourth Congress of the Paediatricians in Macedonia with international participation, was to achieve a bigger turnout, thus obtaining greater success in rising the awareness of the existence of Primary Immunodeficiency among the general practise doctors,

specialists and even wider. This time, among the guests members of the J-Project from Hungary (Marodi L.), Poland (Bernatowska E., Pac M., Kurenko-Deptuch M.), Romania (Bataneant M.), Bulgaria (Baltadjieva D., Petrova G.) and Serbia (Pasic S.), for the first time, and to our great pleasure, our colleague Sulcebe G. from the University of Tirana, Albania, attended and participated in the event. The auditorium was attended by about 50 participants of the Paediatricians' Congress which enriched the importance of this meeting. The major topic of the meeting was:

"Genetic diagnosis and complex management of patients suffering from primary immunodeficiency in East Europe"

The meeting was organised as a symposium, consisting of two sessions, in which the files of the PID patients in each country, the opportunities of the laboratories in the appropriate centres, the diagnostic and therapeutic aspects and problems in treating the patients were presented. Some cases of PID patients which create diagnostic problem and demand complex management in their handling were introduced. The discussions which commenced during the lectures, endured during the social programme of the stay, presenting an opportunity for socializing and informal debates, thus exchanging experiences and information of the latest diagnostic and therapeutic achievements in the vast area of East Europe.

At the beginning of the meeting, in front of the entrance of the conference room, different materials, both in textual and in pictorial form, which included pamphlets titled "PID- what you should know and what you can do", posters showing the 10 warning signs for PID, were distributed to all the present people. These materials were compelled (translated, printed and distributed in all the medical centres and institutions throughout the country) by the Macedonian working team for Primary Immunodeficiency (Peova, Mironska, Kareva, Stavric), in cooperation with and with the financial aid of Jeffrey Modell Foundation JMF, USA (www.info4pi.org).

A prospective stay in the JM Reference Center in Debrecen of one of our colleagues was arranged with the object of easier cooperation, isolation and sending materials from our PID patients for genetic analysis.

The symposium was held in friendly yet professional atmosphere. It was rated as successful and it completely justified the purpose of its taking place.

We want to express our deepest appreciation to all the participants of this meeting as well as to our sponsors Alkaloid, Makedonija Lek and Replek Farm, who helped its realization.

Kristina MIRONSKA

Kristina Mironska (R; Skopje), Ewa Bernatowska (M; Warsaw), and Srdjan Pasic (L; Belgrade) co-charing a session.

Call for collaboration

Start up of the "immune phenotyping in immunodeficiency" (IPID) platform under the hospices of the Clinical working party of the ESID

Immune phenotyping has been used for a long time for the classification of PID. Thus SCID was divided in T-B- and T-B+ SCID. In Bruton's agammaglobulinemia the absence of B cells was an additional hallmark of the disease. Within the last 10 years the combination of several surface markers allowed subtyping human T and B lymphocytes much more precisely. The homeostasis of these lymphocyte subpopulations is regulated fairly tightly in healthy individuals. Changes of this homeostasis have been described for several PIDs. We and others have found several abnormalities in the circulating B and T cells of patients with CVID ([1-5]. In a similar way specific aberrations have been linked to ALPS (expansion of double negative T cells [6], XLP (expansion of transitional B cells, lack of NKT cells [7;8]), WAS [9] and many more.

In order to define immune homeostasis in various PID, to standardize the staining protocol, to provide diagnostic guidelines for phenotyping the various PIDs I would like to suggest the institution of a platform "Immune phenotyping in Immunodeficiency" (IPID) under the hospices of the clinical working party of the ESID. I have attached our current protocol for phenotyping T and B cell subpopulations. Long term goals of this endeavour are to develop new markers for phenotyping, to characterize and include other immune cells like dendritic cells, monocytes, NK cells, etc., to provide teaching for new centers etc.. I strongly feel that the clinical working party of the ESID is an ideal environment to combine our efforts to typify the different forms of immune dysregulation in PID. Therefore I would like to invite you to contact me at Klaus.warnatz@uniklinik-freiburg.de before 30.4.2004 if you are interested in joining the IPID platform.
Our primary tasks will be to set up a network under the ESID web page which will serve as a board for discussion and updates on the current suggestions. I am happy to arrange a first joined meeting in 2008, as soon as I have a feed back of people interested.

Primary goals:
set up reference centers
Definition of a panel of antibody combinations to define circulating T and B cell subsets
Definition of normal ranges for adults and children (age dependent)
selection of the first PID to analyze
to acquire funding

Looking forward to our collaboration, with best regards

Klaus WARNATZ

References

1. Warnatz K, Denz A, Drager R, Braun M, Groth C, Wolff-Vorbeck G, Eibel H, Schlesier M, Peter HH: Severe deficiency of switched memory B cells (CD27(+)IgM(-)IgD(-)) in subgroups of patients with common variable immunodeficiency: a new approach to classify a heterogeneous disease. Blood 2002, 99:1544-1551.
2. Wehr C, Kivioja T, Schmitt C, Ferry B, Witte T, Eren E, Vlkova M, Hernandez M, Detkova D, Bos PR, Poerksen G, von BH, Baumann U, Goldacker S, Gutenberger S, Schlesier M, Bergeron-van der CF, Le GM, Debre P, Jacobs R, Jones J, Bateman E, Litzman J, van Hagen PM, Plebani A, Schmidt RE, Thon V, Quinti I, Espanol T, Webster AD, Chapel H, Vihinen M, Oksenhendler E, Peter HH, Warnatz K: The EUROclass trial: defining subgroups in common variable immunodeficiency. Blood 2007.
3. Piqueras B, Lavenu-Bombled C, Galicier L, Bergeron-van der Cruyssen F, Mouthon L, Chevret S, Debre P, Schmitt C, Oksenhendler E: Common variable immunodeficiency patient classification based on impaired B cell memory differentiation correlates with clinical aspects. J.Clin.Immunol. 2003, 23:385-400.
4. Vlkova M, Thon V, Sarfyova M, Blaha L, Svobodnik A, Lokaj J, Litzman J: Age dependency and mutual relations in T and B lymphocyte abnormalities in common variable immunodeficiency patients.

Clin.Exp.Immunol. 2006, 143:373-379.

5. Giovannetti A, Pierdominici M, Mazzetta F, Marziali M, Renzi C, Mileo AM, De FM, Mora B, Esposito A, Carello R, Pizzuti A, Paggi MG, Paganelli R, Malorni W, Aiuti F: Unravelling the complexity of T cell abnormalities in common variable immunodeficiency. J.Immunol. 2007, 178:3932-3943.

6. Simon HU, Yousefi S, Dommann-Scherrer CC, Zimmermann DR, Bauer S, Barandun J, Blaser K: Expansion of cytokine-producing CD4-CD8- T cells associated with abnormal Fas expression and hypereosinophilia. J.Exp.Med. 1996, 183:1071-1082.

7. Cuss AK, Avery DT, Cannons JL, Yu LJ, Nichols KE, Shaw PJ, Tangye SG: Expansion of functionally immature transitional B cells is associated with human-immunodeficient states characterized by impaired humoral immunity. J.Immunol. 2006, 176:1506-1516.

8. Nichols KE, Hom J, Gong SY, Ganguly A, Ma CS, Cannons JL, Tangye SG, Schwartzberg PL, Koretzky GA, Stein PL: Regulation of NKT cell development by SAP, the protein defective in XLP. Nat.Med. 2005, 11:340-345.

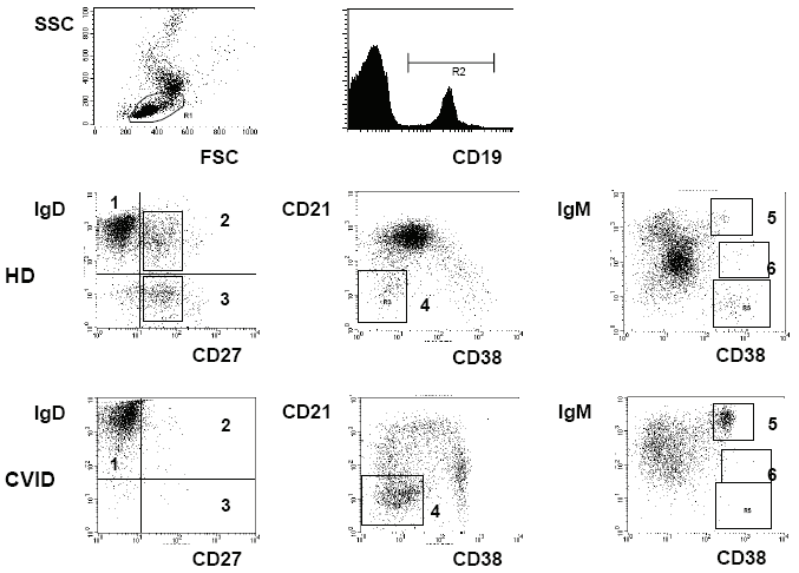
9. Park JY, Shcherbina A, Rosen FS, Prodeus AP, Remold-O'Donnell E: Phenotypic perturbation of B cells in the Wiskott-Aldrich syndrome. Clin.Exp.Immunol. 2005, 139:297-305.

The proposed phenotyping protocols:

T cell phenotyping

field name	explanatory text	dimension (s)	additional menu	suggested frequency	minimum frequency	DocumentationStatus	Comments
Leukocytes	Including differential blood count	absol. (/µl)	1)	1x		mandatory	
T cell phenotyping				Four Stainings: 1) CD45RO Fitc/CXCR5 PE/CD3 PerCP/CD4 APC 2) CD27 Fitc/ CD28 PE / CD3 PerCP/CD8 APC 3) CD45RA Fitc/CD31 PE/CD3 PerCP/CD4 APC 4) CD8 Fitc/TCRαβ PE/CD3 PerCP/CD4APC		
CD3 total	Total T cells	% lymphocyte AND absol. (/µl)	1)	1x		mandatory	Repetitive measurements need to be discussed
CD4	CD4 T cells	% T cells AND absol. (/µl)	1)	1x		mandatory	
CD8	CD8 T Cells	% T cells AND absol. (/µl)	2)	1x		mandatory	
CD3+CD4/8-	Double negative T cells	% T cells AND absol. (/µl)	4)	1x		mandatory	γδ T cells=100-αβT cells
CD4 CD45RO	CD4 memory T cells	% CD4 T cells + absol. (/µl)	1)	1x		mandatory	
CD4 CD45RO CXCR5+	Circulating CXCR5+ CD 4 T cells	%CD4 CD45RO T cells	1)	1x		mandatory	
CD4 CD45RA CD31+	CD4+ Recent thymic emigrants	% CD4 T cells + absol. (/µl)	3)	1x		optional	
CD8 CD27- CD28-	Late CD8 effector T cells	% CD8 T cells + absol. (/µl)	2)	1x		mandatory	
CD8 CD27+ CD28-	CD8 effector T cells	% CD8 T cells + absol. (/µl)	2)	1x		mandatory	
CD4 CD25hi CD127-	CD4 T regs (CD45RO/CD127/CD4/CD25)	% CD8 T cells + absol. (/µl)	extra	1x		optional	

B cell phenotyping



1 naive B cells
2 MZ B cells
3 sw mem B cells
4 CD21^{low} B cells
5 transitional B cells
6 plasmablasts (switched + IgM)

B cell phenotyping

field name	explanatory text	dimension (s)	additional menu	suggested frequency	minimum frequency	Documentation Status	Comments
Leukocytes	Including differential blood count	absol. (/µl)			always	mandatory	
Lymphocyte sub-populations 1	T cells (absolute)	% lymphocyte + absol. (/µl)	CD8Fitc/CD4PE/ CD45PerCP/CD3APC		always	mandatory	Whole blood assay
Lymphocyte sub-populations 2	B cells, NK cells (absolute)	% lymphocyte + absol. (/µl)	CD19Fitc/CD16,56PE/ CD45PerCP/CD3APC		always	mandatory	Whole blood assay
B cell phenotyping				Two Stainings: 1) CD27 Fitc/IgD PE/CD19 Pc7/IgM Cy5 2) CD21 Fitc/ CD38 PE / CD19 Pc7/IgM Cy5 3) Kappa FITC/Lambda PE/CD19Pc7/IgM Cy5			
CD19 Total	Total B cells	% lymphocyte + absol. (/µl)	1)	1x		mandatory	Repetitive measurements need to be discussed
CD27- IgM+ IgD+	Naïve B cells	% B cells AND absol. (/µl)	1)	1x		mandatory	
CD27+ IgM+ IgD+	IgM mem / Marg. zone B cells	% B cells AND absol. (/µl)	1)	1x		mandatory	
CD27+ IgM- IgD-	Switched mem, post GC B cells	% B cells AND absol. (/µl)	1)	1x		mandatory	
CD38++ IgM ++	Transitional B cells	% B cells AND absol. (/µl)	2)	1x		mandatory	
CD38+++ IgM (+)/-	Plasmablasts	% B cells AND absol. (/µl)	2)	1x		mandatory	
CD21low CD38 low	CD21 low B cells	% B cells AND absol. (/µl)	2)	1x		mandatory	
Kappa/lambda	Exclusion of monoclonal population	Ratio	3)	1x		mandatory	Repeat in case of suspected lymphoma
OTHERS							

Comment: The Lymphocyte subpopulations 1 and 2 (whole blood) are necessary to determine absolute numbers of all the other subpopulations. Gate on CD45 positive cells and lymphocyte gate.
When separation of IgM plasmablasts and transitional cells not possible. additional staining with CD20 instead of CD19 may be necessary.

Working Party reports

Educational WP

The Educational Working Party has now reviewed the feedback from the 2007 ESID Summer School and is busy planning the Educational Day which will take place on Thursday 16 October (the day before the main ESID Meeting in 2008 in 's-Hertogenbosch, The Netherlands). We are looking to have a fun and stimulating day with lots of participation from ESID juniors and plenty of lively interaction with the Faculty. We hope to have an opportunity for poster sessions and discussion, as well as "state of the art" mini lectures and case presentations. ESID seniors will be welcome . . . so long as there is first room for all the juniors, and seniors don't interrupt too much! :-)

We are also thinking ahead to the next Summer School in 2009 as we want to be in good time to secure the right venue. We are hoping to hold the Summer School in Eastern Europe - more will be announced in due course!

Finally, we are still awaiting applications for the 10,000 Euros ESID Educational Working Party Scholarship that was announced in the last ESID newsletter. Although the official deadline of 1 December '07 has passed, we are still welcoming applications for this wonderful opportunity for a trainee to visit another centre to pursue a research project; a mind broadening opportunity. Please refer to the previous advertisement for further details, or contact Prof Andrew J Cant via e-mail: Gale.Roberts@nuth.nhs.uk.

Andrew CANT

Registries WP

Registration progress

In 2007, the progress in documented cases in the ESID Online Database was more than satisfactory. After patient numbers had already doubled in 2006, they almost did so again in 2007, from 3,047 patients to 5,504 patients as of today, which makes an increase of 2,457 patients or 81%. We are also very content about follow-up documentation which ranges between 50% and 70% depending on the different countries. Follow-up documentation is a very important aspect of the ESID Database. Therefore, we encourage all centres which have not updated their patients in the last year to do so in 2008.

Reporting Tool

While it is already possible for database users to download report sheets for single patients directly through the web interface, it is not possible to run complex queries on the data.
Therefore, it has been decided to create a separate reporting tool. We are currently developing this tool which is going to be available to users within the next two months.
Users will be able to run their own queries. Parameters can be entered as free text (e.g. lab values) or chosen from drop down menus. We will inform the users as soon as the system is available online.
Any input for the further development, especially suggestions for queries to be implemented, are welcome.

Data quality

ESID has a big interest in maintaining the data quality in the ESID Online Database. After already having implemented several major changes in mid-2007, we made another major change to the

Core Dataset recently by refining the medication modules. There are now three separate sections for medications, one for Ig-replacement, one for Antibiotics (being the most frequent medications used in PID) and one section for other kinds of medication. By offering this new structure, it is much easier to maintain (and control) the data quality, especially for Ig-replacement. Fig. 2 shows a screenshot of the section for Ig-replacement. It is now only necessary to select the brand name from a limited list of entries, and users can choose to enter the dose either absolutely or in relation to body weight. Further measures to enhance data quality, such as additional validation tools and on-site data checks will be established in the coming year. We are also working on means of facilitating the complete documentation of all desired values e.g. through cross checks and reminders.

The ESID Regostries Working Party is looking forward to good collaboration with all documenting centres and the ESID community in 2008 !

Gerhard KINDLE

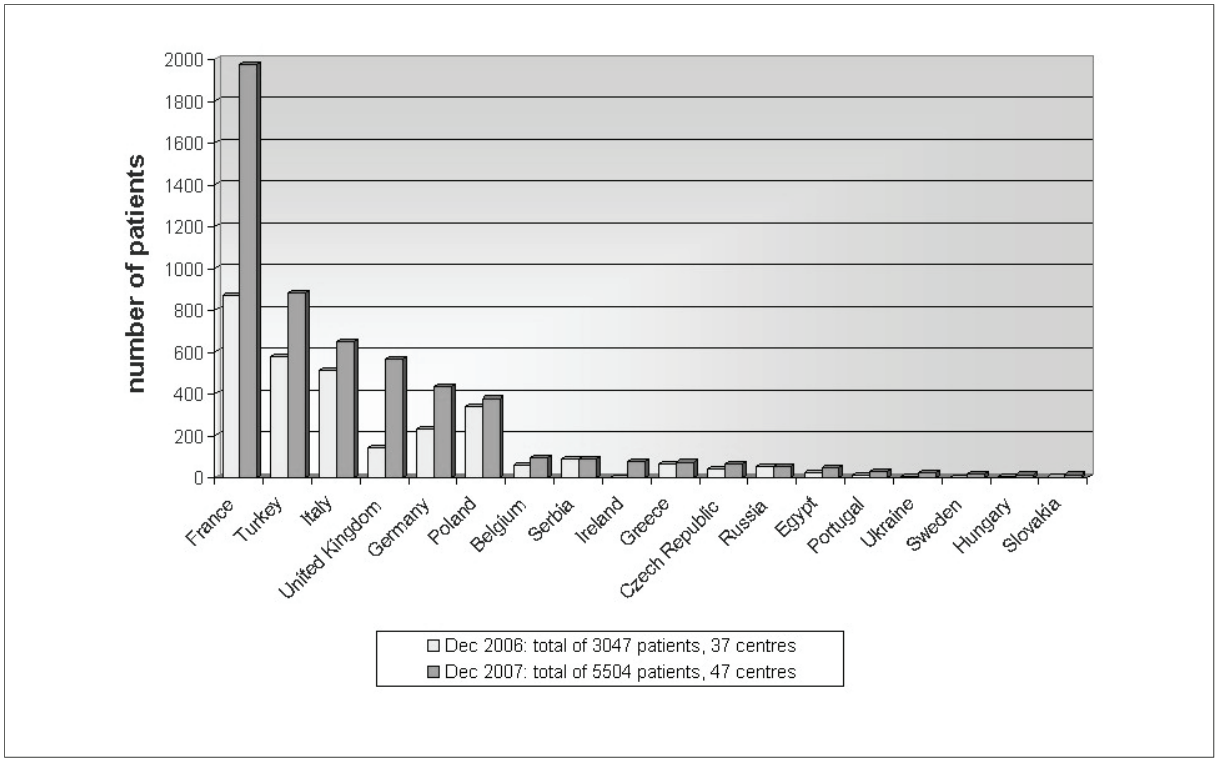


Fig 1: Patients registered in the ESID Online Database, December 2006 and December 2007 compared. Only countries with more than 10 patients are shown.

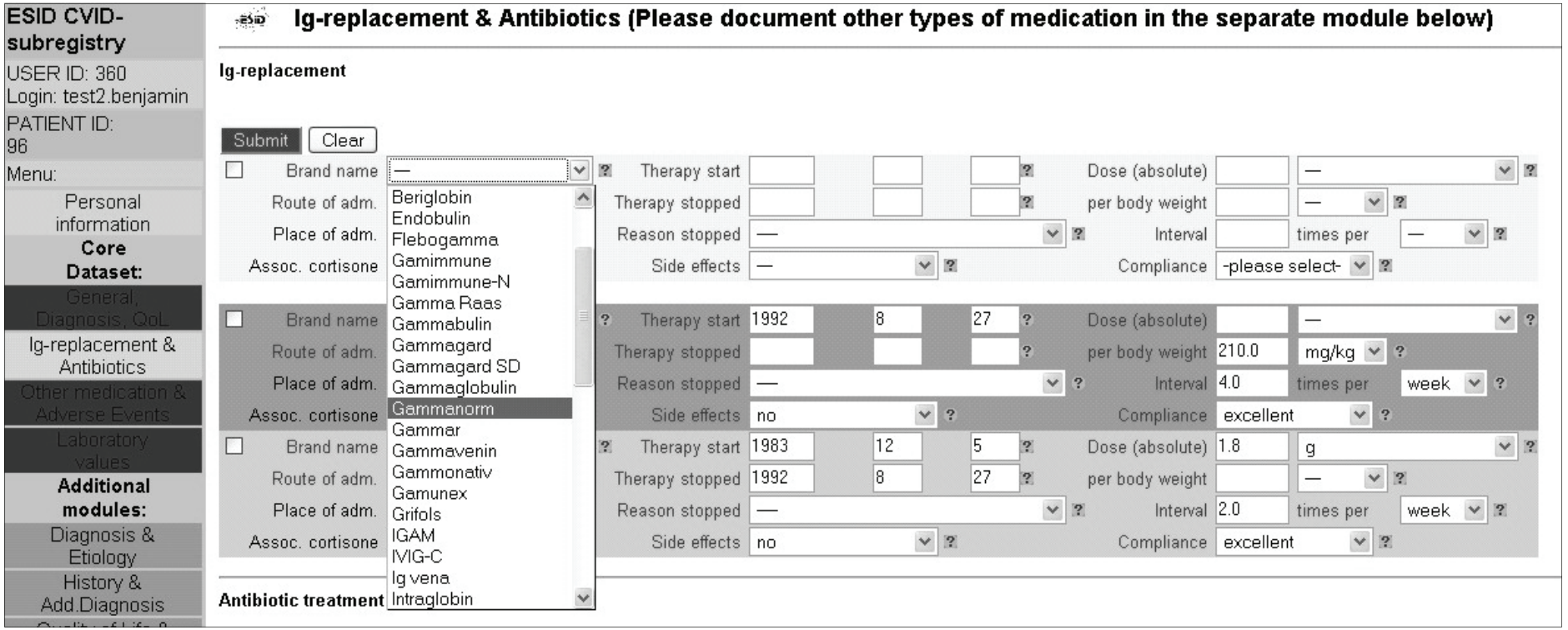


Fig 2: Screenshot of Core Dataset/Ig-replacement section.

Studies initiated via and using the ESID Online Database

Title	Head of study	Status	Initiation	Centres contacted	Centres interested
XLT (WASP) Survey	Michael Albert	Running	July 2007	All	
XLA (Btk.)	Edward Smith	Subregistry complete, Study goals on website, Status unknown	11 Oct 2006	25	20
HAX1 mutations in SCN patients	Bodo Grimbacher, Christoph Klein	Centres contacted, status unknown	12 Oct 2006	5	3
CVID patients with HIGM	Anne Durandy	Database only used for finding patients?, status unknown	3-nov-06	14	11
CVID/MBL	Vojtech Thon	Evaluation	nov-06		
CVID - 10 most burning questions	Bodo Grimbacher	Final modifications to dataset	waiting		
CD40L with NEC	Laszlo Marodi	Database only used for finding patients		All	
FOXN1	Claudio Pignata	Only core dataset	waiting		
NBS	Ewa Bernatowska	Subregistry complete, Study goals on Website, Status unknown	waiting	All	
DGS	Anna Sediva	Subregistry complete	waiting		
CD3	José R. Regueiro	SCID subreg. demo	waiting		
WAS	Adrian Thrasher?	Subregistry draft	waiting		
CGD	Taco Kuijpers, Merlijn van den Berg	Subregistry draft	waiting		

Overview of ESID studies initiated via and using the ESID online database

Juniors WP

Dear ESID Juniors,

I hope you all spent a great Holiday Season!

Here is a brief update on our activities:

- Sponsor money for funding "Short-Term Stay Program" will be available shortly. Details will follow soon and will be posted on the website.

- We are finally working on implementing the junior section of ESID website with our latest activities! At this point your suggestions and inputs will be really important so please email me and let me know if you would like to post something on the website (i.e. Ales and Lucia, would you like to post your Newsletter sections in there as well?)

- Together with the Educational Working Party we are planning of a "new shaped" Educational Day within the 2008 ESID meeting. Junior members will actively take part with oral presentations or posters on clinical cases or research activities…More details will be available with the second announcement of the meeting! I am very much looking forward it!!!

Have a super winter!

Eleonora GAMBINERI

Interesting Cases

The clinical riddle
peculiar or unresolved cases provided by ESIDJuniors

Case #5: Lactogenic hypozincaemia leading to acrodermatitis enteropathica and impaired polymorphonuclear cells function.

We briefly present a case of a girl that was born prematurely in the 31st week of gestation due to mother´s preeclampsia (birth weight was 1280g). The mother is of Caucasian and the father of sub-saharian origin . The delivery and the early postnatal period were uneventful. Parenteral nutrition was employed because of the prematurity of the baby, however, during a few days it was gradually tapered, and oral feeding with mother's milk was initiated. The girl was breast-fed – fully for 7 months, partially until the age of 18 months.

At the age of 2 months skin vesicular exanthema on the face and the perianal area appeared. Locally administered antimycotic therapy and other topical treatment were ineffective. Two weeks later skin bacterial superinfection appeared and hospital admission was inevitable. The erythematous, scaly, erosive patches, papules and tiny vesicles on the face and perilabial region, acral parts of upper and lower limbs, lower back, buttocks were present. The most severe lesions were in perigenital and perianal area. The baby was not well, restless, refusing fluids, suffering from abdominal pain and diarrhoea.

The biochemical laboratory investigation of blood was unremarkable, apart from profound zinc deficiency (1.6 µmol/l, NR 9-16 µmol/l). Zinc concentration was measured in her mother as well – the blood level was normal (14.7 µmol/l), whereas the level in her milk was bellow normal range (2.4 µmol/l, NR in controls 3.8-10.2 µmol/l).

The immunological analyses at the time of diagnosis revealed hypogamaglobulinaemia - IgG 1.6 g/l (NR 2.5-7.5), IgA 0.07 g/l (NR 0.08-0.8), IgM 0.31 g/l (NR 0.1-0.7) and remarkably decreased polymorphonuclear cells (PMNs) function. Nitroblue tetrazolium (NBT) dye test showed significant reduction in oxygen radical intermediates production (<1% positive granulocytes, NR > 9%). The defect was also reflected in decreased chemiluminiscence, which was about 30% of that seen in normal controls. Myeloperoxidase deficiency was excluded. Other immunological parameters were within normal limits. Intermittent neutropenia was recorded (but not in the time when NBT and chemiluniscence tests were performed), no lymphopenia was documented.

After exclusion of other causes, the diagnosis of lactogenic acrodermatitis enteropathica was made and oral zinc supplementation was initiated. Zinc level normalized rapidly,
marked clinical improvement was observed within a few days; complete resolution of the skin lesions was documented after 9 days of therapy.

NBT dye test and chemiluniscence normalized at the age of 19 months and remains normal thereafter. Normal production of reactive oxygen intermediates during respiratory burst measured by flow cytometry using DHR 123 dye was documented at the age of 23 months, mild hypogamaglobulinaemia has been persistent.

Currently, at the age of 23 months, the girl is thriving well with normal psychomotor development. Apart from the skin problems the girl has not suffered from

any infections.

Discussion

Zinc is an important trace element for DNA and RNA metabolism, it is involved in signal transduction, gene expression, and apoptosis. Every highly proliferating cell system is dependent on sufficient availability of zinc. Thus, also the immune system could be significantly affected by its deficiency. Zinc is important for the innate part of the immune response e.g. for recruitment, chemotaxis and phagocytosis of neutrophils and monocyte-derived cells and NK cells cytotoxicity, as well as for the specific one. Zinc deficiency is associated with decreased number of B and T cell precursors, impaired antibody response (mainly against T-cell dependent antigens), reduced production of naive CD4+ cells and decreased T-cell proliferation after mitogen stimulation; production of pro-inflammatory cytokines is affected and increased autoreactivity of T cells is suspected due to thymic malfunction. In the affected patient, zinc deficiency may lead to increased incidence of infections, impaired wound healing and possible autoimmune disease. Conversely, high doses of zinc may have detrimental effect on immune system as well, especially on T cells.

Acrodermatitis enteropathica is a rare genetic or acquired disorder caused by hypozincaemia. One of the causes of secondary hypozincaemia is prematurity as the premature infants require more zinc than normal-term newborns and the breast-feeding might be insufficient source of this trace element as it was in the case of our patient.

Regarding the phagocytosis, impaired production of reactive oxygen metabolites needed during the respiratory burst has been demonstrated in zinc deficient mice as well as in humans. However, the time needed to restoration of normal phagocytic activity after zinc supplementation has not been clearly demonstrated. We saw that in contrast to rapid disappearance of the skin eruptions, normalization of the laboratory parameters reflecting production of oxygen radicals took a few months, however, with no impact on the clinical status of the patient.

Our remark is that zinc deficiency may lead to prolonged impairment of PMNs functions
and possibly mild hypogamaglobulinaemia. On the other hand, we also want to remind that attention should be paid to zinc level status while investigating breast-fed infant with skin lesions, chronic diarrhoea and/or immunological abnormalities, namely decreased phagocytic activity.

Aleš JANDA
Anna ŠEDIVÁ

We wish to thank Dr Tomáš Honzík for providing detailed patient data.

References:

1. Ibs KH, Rink L. Zinc-altered immune function. J Nutr. May 2003;133 (5 Suppl 1):1452S-1456S.
2. Prasad AS. Zinc: mechanisms of host defense. J Nutr. May 2007;137 (5):1345-1349.
3. Rink L, Gabriel P. Extracellular and immunological actions of zinc. Biometals. Sep-Dec 2001;14(3-4):367-383.
4. Tone K, Suzuki T, Todoroki T. Influence of zinc deficiency on phagocytosis in mice. Kitasato Arch Exp Med. Dec 1991;64(4):263-269.

NK-CELL CYTOTOXIC ASSAYS

Natural killer (NK) cells are a subset of lymphocytes that play a central role in the innate immune response to tumors and infections. Activities of these lymphocyte subset may be impaired or enhanced in disease. Cell-mediated cytotoxicity is the mechanism used by NK cells for defense against intracellular pathogens, tumor cells, and allogeneic tissue grafts. NK cells recognize and kill targets by direct cell-to-cell interactions, cytokine production and/or granule exocytosis. An important limitation in the field of NK research is attributable to the deficit of assays available for the detection of the functional activity of NK cells.

Since 1968, the radioactive chromium-release method (51Cr-release assay, CRA) has been traditionally used to determine the cytolytic activity of effector cell populations. Recently, flow cytometry-based methods have been developed to overcome some of the disadvantages and limitations of the CRA.

51chromium-release assay (CRA)

Briefly, target cells are labeled with 100 µCi of 51Cr (Perkin Elmer, Billerica, MA 200–500 mCi/mg) for 1 h at 37 °C in the atmosphere of 5% CO2 in air. The labeled cells are washed twice in complete medium, resuspended in complete medium, and the viable cell counts are performed. Cells are co-incubated at effector to target (E:T) ratios of 50, 25, 12, 6 for use in NK-cell assays. Co-cultures are set up in 24 well flat bottom plates and plates are incubated in triplicate for 4 h to 16 h. The culture supernatants are quantified for 51Cr radioactivity released from lysed targets in an Automatic Gamma Counter. The percentage of cytotoxic activity is calculated using the following formula: % specific lysis = (sample cpm–spontaneous cpm)/(maximal cpm–spontaneous cpm)×100%.

Four-color flow cytometry-based cytotoxicity assay (FCC)

Target cells are labeled with 5 µM CellTracker Orange CMTMR (CTO) (Invitrogen, Eugene, Oregon) for 1 h at 37°C in the atmosphere of 5% CO2 in air. Peripheral blood mononuclear cells (PBMCs) are incubated in the presence of FITC-anti-CD16 (Leu-11a) (BD Biosciences, San Jose, CA), FITC-anti-CD56 (NCAM16.2) (BD Biosciences), and ECD-anti-CD3 (UCHT1) (Beckman Coulter, Miami, FL) monoclonal antibodies (MoAbs) according to the manufacturers' recommendations for 30 min at 4°C. The effector cells are co-incubated at the E:T ratios of 50, 25, 12, 6 for NK cell. Triplicate samples are set up for each E:T ratio. As controls, targets or PBMCs alone are incubated in complete medium to measure spontaneous cell death. 7-amino-actinomycin D (7-AAD) (BD Biosciences) is added to every tube at the final concentration of 1 µg/mL, as recommended by the manufacturer. Fluorospheres (Beckman Coulter) are added in order to obtain absolute cell counts. In parallel to tubes set up for measurements of cytotoxicity, PBMCs are incubated in the presence of anti -CD3, -CD16, and -CD56 MoAbs. The cells are coincubated at the E:T ratios of 50, 25, 12, 6 for the NK-cell assay at 37°C in the atmosphere of 5%CO2 in air. To identify effector cells activated in the presence of the target, FITC-anti-CD69 (BD Biosciences) MoAb is added to the assay tubes immediately after termination of the incubation period. The cells are washed twice in PBS, fixed in 2% (w/v) paraformaldehyde in PBS (PFA) and washed again in PBS. Next, they are permeabilized in 1% saponin/0.1% (v/v) bovine serum albumin (BSA) in PBS (saponin solution), stained with PE-anti-granzyme B MoAb (CLB-GB11) for 30 min at

4°C and washed in saponin solution followed by PBS.

CD107a assay

Recently, lysosomal-associated membrane protein-1 (LAMP-1 or CD107a) has been described as a marker of CD8+ T-cell degranulation following stimulation so the CD107a assay is a degranulation test that is performed by the quantification of cell surface CD107a expression.
NK cells from healthy donors and patients are purified from PBMCs and then are cultured on irradiated feeder cells in the presence of 2 µg/mL phytohemagglutinin (Sigma-Aldrich, Irvine, United Kingdom) and 100 U/mL rIL-2 (Proleukin; Chiron, Emeryville, CA) to obtain proliferation and great expansions of polyclonal NK-cell populations. 2x105 polyclonal NK-cell populations or 24 hour IL-2–activated PBMCs are cocultured with 2x105 target cells (K562, FO-1, 221, or P815 cells) in 96 V-bottom well plates. In each well, containing 200 µL E/T cell suspension, 5 µL PE-conjugated anti-CD107a mAb (BD Pharmingen) are added prior to incubation. Cells are mixed by gentle pipetting and incubated for 2 hours at 37°C in 5% CO2. Thereafter, the cells are collected, washed in PBS, and stained with anti–CD3-FITC and anti–CD56-PC5 mAbs for flow cytometric analysis. Surface expression of CD107a is assessed in the CD56+ cell fraction of either CD3- PBMCs or polyclonal NK-cell populations.

COMMENTS

Although the CRA is reliable and has become a "gold standard" for measuring cytotoxicity, it has a number of disadvantages and functional limitations: (1) the use of radioactivity which may be hazardous to health and is impractical and costly due to the short half-life of 51Cr and requirements for radiation safety training and licensing; (2) the use of CRA is limited to targets which spontaneously label with 51Cr quantities sufficient for reliable detection of lysis; (3) the CRA sensitivity depends on the background; (4) the assay is not interpretable if spontaneous 51Cr-release is high, and thus many targets are not suitable for CRA because of high spontaneous 51Cr release; (5) its interassay variability is considerable. The functional limitations of the assay are that results are uniparametric, death is not quantified at a single-cell level, and difficulties in labeling target cells with 51Cr are common.

The ability of effector cells to kill a target expressing certain defined characteristics has become an accepted way of monitoring cytotoxic activity. At the same time, the nature as well as numbers and phenotypic characteristics of effector cells mediating this activity are of interest to fully evaluate the extent of abnormalities present in disease or recovery of effector cell functions following therapy.

The FCC assay is a multi-color flow cytometry assay to simultaneously measure NK cell-mediated cytotoxicity, visualize conjugates of tumor and effectors, obtain absolute cell counts, measure cytolytic function of killer cells and determine their immunophenotype. In addition FCC assay is more sensitive and has a minor coefficient of variation than the CRA, and reliably measures NK cell- mediated killing of target cells in normal controls and subjects with cancer. The FCC assay can be used to study a range of phenotypic attributes, in addition to lytic activity of various subsets of effector cells, without radioactive tracers and it is relatively inexpensive. The FCC assay has a potential for providing information about molecular interactions underlying target cell lysis and thus becoming a major tool for studies of disease pathogenesis as well as development

of novel immune therapies.

CD107a is a marker of NK cell functional activity and it is significantly upregulated on the surface of NK cells following stimulation with MHC devoid targets. Additionally, CD107a expression correlates with both cytokine secretion and NK cell-mediated lysis of target cells. However, as well as being coordinately expressed on nearly all cytokine secreting cells, CD107a was also expressed on a large subset of NK cells that did not secrete cytokine following stimulation. These data suggest that employing CD107a as a marker of NK cell functional activity may allow for the identification of a large fraction of activated NK cells that may degranulate in the absence of cytokine secretion.

What do you think about these methods? (l.bianchi@meyer.it)

Lucia BIANCHI

REFERENCES

Whiteside TL, Bryant J, Day R, Herberman RB. Natural killer cytotoxicity in the diagnosis of immune dysfunction: criteria for a reproducible assay. Journal of Clinical Laboratory Analysis 4: 102-114, 1990.

Alter G, Malenfant JM, Altfeld M. CD107a as a functional marker for the identification of natural killer cell activity. Journal of Immunological Methods 294:15–22, 2004.

Marcenaro S, Gallo F, Martini S, Santoro A, Griffiths GM, Arico´ M, Moretta L, Pende D. Analysis of natural killer–cell function in familial hemophagocytic lymphohistiocytosis (FHL): defective CD107a surface expression heralds Munc13-4 defect and discriminates between genetic subtypes of the disease. Blood 108:2316-2323, 2006.

Kim GG, Donnenberg VS, Donnenberg AD, Gooding W, Whiteside TL. A novel multiparametric flow cytometry-based cytotoxicity assay simultaneously immunophenotypes effector cells: Comparisons to a 4 h 51Cr-release assay. Journal of Immunological Methods 325:51–66, 2007.

PID-care in development:

Morocco

Can you give me some information about your background and can you tell me something about your career history?

My name is Aziz Bousfiha, I was born in 1963 in Kenitra, a small town on the Moroccan side of the Atlantic Ocean. I am currently married and have two children. I did my medical studies at the Rabat Faculty of Medicine until I joined, in 1988, the Casablanca Faculty of Medicine as resident in pediatrics.

Before I began my training in Paediatrics at the Children's Hospital, I first spent a year in the immunology laboratory where I prepared my PhD in Medicine on the immunological features of celiac disease through a series of 41 children. With my team, we had studied the HLA typing A and B (we confirmed the association of celiac disease with HLA-B8 in Morocco), autoimmunity, food allergy, lymphocyte populations and determination of serum immunoglobulins in this disease.

At the end of this training I joined the pediatric hematology-oncology team in the Children Hospital of Casablanca and I did an internship at the Gustave Roussy Institute in Paris. I worked on the Moroccan leukaemia immunostaining of the

child, on syndrome among chromosomal fragile. In 1996, I joined the pediatric infectious diseases team in the Casablanca children hospital where I cared for children with Primary Immunodeficiencies and in 1997, I did an internship in pediatric Immunohematology unit at the Necker-Enfants malades Hospital (Prof. Alain Fischer) where I worked under the supervision of Professor Stephane Blanche and Doctor Jean-Laurent Casanova, then a clinical and research fellow in the service. Thereafter, I participated in the creation of the Clinic Unit Immunology of our hospital and was given his leadership since 1997.

Can you give me some information about health care in your country?

The Kingdom of Morocco is a beautiful country located in the northwest of Africa, on the edge of Europe. Its geography is marked by two chains of Mountains: the Atlas and the Rif. Underneath the Atlas begins the Sahara desert. In 2005, the total population was 31.478.000 with a gross national income per capita $ 4360. Life expectancy at birth is 69/73 years, but the quotient of infant mortality (per 1000 live births) is 40. The total expenditure on health per capita is $ 234, or 5.1% of gross domestic product.

Public health covers basic care of the vast majority of the population. The liberal sector, well-developed in major cities, offers a care of quality but care is very expensive. There are clear differences between care in the cities and those in rural areas, where the poor people typically have difficulties in gaining access to a medical care of quality. An effort is currently undertaken by the government, including doubling the number of doctors trained. Social security is still underdeveloped but recently has been installed compulsory health insurance that covers, among other things, all the care of children from birth to 12 years. There are currently 4 university hospital centre (Casablanca, Rabat, Fez, Marrakech), which comprise only two hospitals for children (Casablanca and Rabat), which both include services of pediatric hematology-oncology. The Centre in Casablanca has the only PID centre in the kingdom, the Clinical Immunology Unit where I work and where I am in charge of children with PIDs.

Can you give me some information about PID-care in your country?

During the 80's, the Laboratory of Immunology proposed explorations as a basis for the diagnosis of PID, including weight filling immunoglobulins, numeration of lymphocyte sub-populations, NBT, CH50. Unfortunately, there was no clinical respondent. The result was no or very few patients until 1997. During this year, was founded Unit Clinical Immunology in the department of paediatric infectious diseases, but the laboratory of immunology has restricted its explorations of PID, for lack of demand…

The first few years, we have made assessments in the Liberal area and sub lymphocyte populations were treated in laboratories in France. The high cost of these explorations, in addition to the cost of treatment, pushed us to create the association 'Hajar' to support the care of children with PID. Hajar was the first girl with HLA-II deficiency and we invested much effort to save her. Unfortunately, she has left us but she has brought together doctors and benefactors to create this association (www.hajar.org.ma).

After several connections with the hospital to buy a flow cytometer in the

laboratory of immunology, children of the Hajar Association and their parents have contacted in 2001 the director of the hospital who purchased such equipment. Currently, the weight filling immunoglobulins and the counting of lymphocyte sub-populations are available at the hospital but the CH50 is determined in the Liberal and NBT has been developed in the laboratory of immunology at the Faculty of Sciences. Alongside these modest efforts, collaborations were established with laboratories in Europe, in particular the reference centre of PID (Françoise Le Deist, then Capucine Picard) and the Laboratory of Human Genetics of Infectious Diseases (Jean-Laurent Casanova and Laurent Abel). Thus, functional analysis and molecular biology were made for the sick. We also collaborate with Anne Durandy (Institut National de la Santé et de la Recherche Médicale (INSERM), U768, Hôpital Necker-Enfants Malades, Paris), Claire Fieschi (Département d'immunologie, Université Paris VII Denis Diderot, AP-HP, Paris), Eric Vivier (Centre d'Immunologie de Marseille-Luminy, Université de la Méditerranée, Marseille 13288, France) etc

The intravenous immunoglobulins are currently available but not yet covered by social security and are therefore inaccessible to a large number of patients. The association Hajar has introduced two solutions: the sponsorship of patients by benefactors and the contribution of up to 50% of the cost. The vial costs 5g DH 1150.00 ($ 115.00). The Hajar association covers much of antibiotics. As for the transplant, allograft is not yet available. The only transplant center, which is located at the Hospital of Casablanca, which currently does autograft but allograft is expected soon. Patients in the unit are grafted, when there were, in Europe, notably in France, Spain and Italy. However, now that patients are here, the future looks better. Recently, the Hajar Association has launched an awareness of the general public and doctors to this pathology.

On medical research, the Clinical Immunology Unit has established the first set of PID: 173 patients. The CID accounted for 20.1%, of which 15 had SCID and 11 had HLA-II deficiency. Deficits dominant antibodies represented 25.3% of which 9 were certainly all autosomal recessive hyperIgM syndrome. The most common deficit is the hyper IgE syndrome with 25 cases followed by ataxia telangiectasia with 19 cases. 8 patients had a MSMD. The clinical and immunological profile of each group of PID has been described and several cases were atypical. Currently we supervise 2 doctoral theses in immunology, one on the genetics of HLA-II deficiency and the other on the immunogenetic profile of CID. Thus, the preliminary results show that we can make an antenatal diagnosis deficit HLA-II, thanks to the collaboration with the Faculty of Science.

How did you become interested in immunodeficiencies?

If I always had a trend and interest in immunology during my medical studies, it is only a set of circumstances that eventually put me on the track of PID. First I was in the laboratory of immunology for my MD thesis; I was in the unity of pediatric hematology-oncology. It is late Professor Abid, head of the department of infectious diseases in children, who proposed to me this case. Seeing in retrospect, I can see that the good Lord has organized my training to care for this pathology in Morocco.

What do you hope to achieve in the future?

1 - Awareness and training : The association Hajar deals with the general public

and helping the Clinical Immunology Unit to ensure awareness among physicians with PID. In fact, one of my main goals is currently contributing to the training of doctors and biologists to PID. I am counting on ESID to help us in this training. Unit Clinical Immunology must now begin its second decade with a frank improvement in the quality of diagnosis and care.

2 - The registration of immunoglobulins in the list of reimbursable drugs and the launching of the allograft.

3 - We must advocate for a better immunological laboratory to monitor the development of clinical PID. The establishment of a specialized laboratory in the PID therefore seems a good solution to meet the demand of clinicians who are now becoming more frequent and confronted with a growing number of patients with a good proportion has multiple clinical and biological atypical. On the other hand, in particular the work of the Laboratory of Human Genetics of Infectious Diseases shows that the PID are currently supporting high metamorphose who will transform from rare diseases to health problems public. Indeed, the PID will find themselves at the centre of the fight against tuberculosis, herpes infections, pneumonia.

4 - Participate in the establishment of ASID the African Society for immunodeficiencies, structure necessary to improve the care specific to PID and defend these patients with governments Africans.

5- Finally, all these measures will help us to better contribute to the international effort in research on the PID. We must develop our research capabilities while strengthening our international collaboration. ESID, again, is a good alienation of the ASID to improve this great international collaboration.

How could ESID help to achieve this goal?

ESID, we welcome the support of officers including the personal involvement of President Jean Laurent Casanova for the creation of the ASID, can help us at several levels:

-- At the level of Morocco, support for the creation of a specialized laboratory in the PID and for the realization of transplants in the European centres. A facilitating access to the school of ESID is highly desirable for young people who are becoming more and more interested in the PID.

-- At the African level, support for the organization of congresses of the ASID whose constituent assembly is planned at the first congress of the ASID, scheduled in Casablanca in fall 2008. In the pre-program, a school of African PID is planned as well as a day on trade between Africans and also between Africans and Europeans in particular.

We hope to build the ASID as a sister society, which would have close links with the ESID on the Northern side of the 'Marenostrum'.

SOCIÉTÉ

10

Aujourd'hui

Mardi 22 Janvier 2008

Les déficits immunitaires primitifs

Le Maroc enregistre 300 nouveaux cas par an

Les déficits immunitaires primitifs qui restent méconnus au Maroc touchent un cas sur 5000 naissances dans le monde. 300 nouveaux cas sont recensés chaque année au Maroc.

Les déficits immunitaires primitifs (DIP) touchent 300 nouveaux cas par an au Maroc. Ils constituent un ensemble hétérogène d'affections caractérisées par une insuffisance primitive des moyens de défense contre les micro-organismes. *«Les DIP, le plus souvent héréditaires affectent le système immunitaire. Les enfants atteints de la maladie souffrent d'infections aiguës et sont très sensibles aux maladies infectieuses»*, affirme à ALM le Pr Ahmed Aziz Bousfiha, président de l'Association Hajar et du Groupe d'étude marocain de déficit immunitaire primitif. Au Maroc, l'incidence des DIP serait plus élevée que dans les pays occidentaux en raison du fort taux de consanguinité qui est de 19,9%. Les DIP regroupent près de 100 maladies héréditaires différentes et peuvent être scindés en quatre groupes : les déficits de l'immunité humorale, les déficits de l'immunité cellulaire, les déficits de l'immunité non spécifique et les déficits immunitaires associés à d'autres affections.

Les déficits immunitaires primitifs qui touchent un cas pour 5.000 naissances dans le monde peuvent apparaître chez des personnes de tout âge.

Les premières descriptions de ces maladies ont été faites chez des enfants ; l'expérience médicale a ensuite permis de diagnostiquer des déficits immunitaires primitifs chez de nombreux adolescents et adultes. Pour faire face à la maladie, le traitement repose essentiellement sur les antibiotiques, les perfusions d'immunoglobulines qui sont des moyens permettant de pallier les dysfonctionnements des anti-corps fabriqués par l'organisme. *«Dans les cas les plus graves, il faut avoir recours à la greffe de la moelle osseuse. Ce type d'opération n'existe malheureusement pas au Maroc et coûte relativement cher. En France, cette opération s'élève à 2 millions de dirhams alors qu'en Espagne et en Italie, elle revient à un million de dirhams. Pour ce qui est des injections, il faut compter 2.500 dirhams et ce à raison d'une injection par mois. Dans ce cas, le malade est dans l'obligation de poursuivre le traitement durant toute sa vie»*, indique Pr Bousfiha. En plus d'un traitement relativement onéreux, il est navrant de constater qu'il existe un seul centre de soins et deux pédiatres spécialisés pour ce type de pathologies dont le Pr Bousfiha et le Pr Fatima Ailal sur tout le Royaume.

La thérapie génique par transfert d'un gène sain capable de suppléer le gène défaillant constitue l'espoir pour guérir les enfants et les adultes atteints par les DIP.

• Lalla Zerrour
lzerrour@aujourdhui.ma

• *Pr Ahmed Aziz Bousfiha, président de l'association Hajar.*

Association Hajar

Créée en 2000, l'Association Hajar d'aide aux enfants aiteints de déficits immunitaires primitifs, ne ménage aucun effort pour soulager ces patients. Hajar est le prénom de la première petite fille qui avait nécessité une greffe de moelle osseuse pour guérir son déficit immunitaire de type HLA II. Malgré des efforts importants de la part des médecins et d'un groupe de bienfaiteurs, HAJAR est morte avant de se faire soigner. Un groupe de personnes de bonne volonté a décidé de réunir les petits patients, leurs parents et quelques bienfaiteurs pour créer cette association. Depuis , ils continuent à soulager et à soigner toutes les personnes ateintes de DIP.

Les déficits immunitaires primitifs

Le Maroc enregistre 300 nouveaux cas par an

Les déficits immunitaires primitifs (DIP) touchent 300 nouveaux cas par an au Maroc. Ils constituent un ensemble hétérogène d'affections caractérisées par une insuffisance primitive des moyens de défense contre les micro-organismes. *«Les DIP, le plus souvent héréditaires affectent le système immunitaire. Les enfants atteints de la maladie souffrent d'infections aiguës et sont très sensibles aux maladies infectieuses»*, affirme à ALM le Pr Ahmed Aziz Bousfiha, président de l'Association Hajar et du Groupe d'étude marocain de déficit immunitaire primitif. Au Maroc, l'incidence des DIP regroupent près de 100 maladies héréditaires différentes et peuvent être scindés en quatre groupes. ■

• Lalla Zerrour
Suite page 16

Morocco