



European Working Group on Gaucher Disease Meeting

Proceedings of the 10th European Working Group on Gaucher Disease (EWGGD)

June 28th-30th 2012
Paris | France

Published by the
European Gaucher Alliance
on behalf of the EWGGD





Dear friends

Helen Michelakakis and myself would like to thank the EGA for collecting the essential information on the Paris 2012 workshop in this dedicated brochure.

The 10th Workshop of the EWGGD (European Working Group on Gaucher Disease) has taken place in summer 2012 at the Novotel Tour d' Eiffel in Paris, France, in a metropolitan surrounding that was certainly avant-garde in the early 70's.

As in the former years, the principal aim of the meeting was to enable a fruitful international scientific exchange on Gaucher-related issues. The opportunity for presenting unpublished scientific data as well as free discussion is a central premise of the Group and was taken to present the forefront of basic research and clinical advances in Gaucher disease.

Most of our patients have successfully managed to cope with the shortage in ERT from June 2009 on, also due to novel and established agents with convincing efficacy. Besides immunological questions, basic disease mechanisms and bone aspects were discussed. Surprisingly, detection and diagnosis of the disease was also a major topic of the conference. Discussion of type 3 disease and Parkinsonism has raised many questions. Novel therapies are ahead for type 1, but still, type 3 is a challenge. We personally enjoyed all invited speakers, but we were especially proud that Roscoe Brady, together with his dedicated wife Bennett, could make it to Paris to share his thoughts on novel therapeutic approaches in this disease. With >270 registered participants, 51 oral presentations and 44 poster presentations it was a successful congregation. We were also able to discuss humanitarian and patient-related aspects of the disease. Further, it was discussed that the European and international nature of the workshop should be advanced. For the future years, more interaction between basic research groups and clinicians would be desired. Still today, although we think that the glucocerebrosidase storage in peripheral tissues is central for the disease pathology, we have no clear idea about the toxic mechanisms in the central nervous system.

During the business meeting Prof. Hans Aerts was awarded with the honorary membership of the association, for his longstanding engagement in Gaucher disease, now being Founder President. In February 2012, the EWGGD has officially been registered in the Netherlands as a daughter organisation of the ESGLD (European Study Group on Lysosomal Diseases) and Marieke Biegstraaten, M. D. and Ph.D., from the Amsterdam Medical Center (AMC) has officially started her work as the association's secretary in November 2011. Mia Horowitz has also been elected to join the executive committee for the next years. Hannah Rosenbaum from Rambam Medical Centre will host the next, the 11th EWGGD workshop in Haifa from June 25-29, 2014, thus keeping up the good tradition to place the EWGGD meeting amidst a major soccer tournament, which will be the World Cup in Brazil.

We truly feel that the 2012 meeting helped to continue the tradition of good scientific quality and was successful to enthuse young physicians and researchers from the whole world in taking care of patients with this disease.

The role of the EGA is increasing and the success of the meeting has inspired us to be forward this association and help increase knowledge on Gauchers disease and thereby improve our patients' lives. We wish you a lot of joy while reading this informative brochure.

Yours very sincerely,

Prof. Stephan vom Dahl,
Chairman EWGGD

Prof. Helen Michelakakis,
Vice Chairman EWGGD



Dear Friends,

As patron of the European Gaucher Alliance I'd like to say 'thank you' for the good cooperation in the past years. Together we fought successfully and achieved a lot for patients suffering from rare diseases and especially patients suffering from Morbus Gaucher.

As you all know, the European Parliament has been committed to improving the therapy of rare diseases for many years. As the spokesman for health policy of the biggest group (EPP) in the European Parliament and the chairman of the working group on Bioethics I have insistently supported and promoted these improvements together with you and your German colleagues. The Regulation on orphan medicinal products as well as the 7th framework programme for research are just two examples of what we have achieved so far together.

But even in the past couple of months we have achieved a lot for the patients. Last month the responsible committee for Research (ITRE) of the European Parliament voted on the Commissions proposal for the new research and innovation program Horizon 2020 (FP 8). Colleagues supported amendments to improve and support research for rare diseases. This text will now be subject to negotiations with Council and Commission and I will insist to keep this proposal inside the final agreement. As another example, in March 2011 the new directive "Patients' rights in cross-border healthcare" entered into force and has to be put into national law until October 25th, 2013. This new directive implements the jurisdiction of the European Court of Justice, which grants every patient the right to be treated abroad and the costs for this treatment to be reimbursed by the national insurances. For patients suffering from rare diseases this means further relief. Through this new directive the member states are obliged to cooperate within so-called European Networks of Reference and to improve the diagnosis of rare diseases, if necessary by transferring patients to neighbouring countries. The European Parliament demanded further improvements for patients suffering from rare diseases, but unfortunately these demands didn't get accepted in the respective negotiations. Nevertheless we can be content with what we have achieved after all. Especially patients suffering from rare diseases need cross-border healthcare more urgently than other patients, because an optimal diagnosis and therapy is often possible only through this very cooperation. Even though health policy is first of all the protection domain of the member states, the fight against rare diseases remains a typical European task, because the number of people suffering from rare diseases is so low compared to the respective total population that information, research activity, diagnosis and sufficient expertise are not available on the national level.

That's why I appreciated and empathically promoted your demand for a European Gaucher-Register at the responsible authorities within the European Commission. The European

(continued overleaf)

(continued from previous page)

Commission acknowledged this demand and initiated the project EPIRARE (Building Consensus and Synergies for the EU Registration of Rare Disease Patients) last year. This is supposed to provide a framework for the cooperation of different registers of rare diseases. This programme is financed by the so-called Health Programme of the European Union. This way there is a secured financing for at least the upcoming two years.

Dear friends, as I have just described, the past years we together achieved once again a lot for the people concerned. Nevertheless, we have to remain attentive and vigilant, because the task of improving the situation of people suffering from rare diseases is and remains an ongoing one. Persuading together will also be crucial in the above mentioned and upcoming negotiations for "Horizon 2020". In order to achieve an optimum for the patients and their relatives, we must continue our proven and well-functioning cooperation here, too. Considering the excellent experiences in the past years, however, I am positive that we will continue this way and achieve together a lot for the patients in the future, as well.

Kind regards



Dr. Peter Liese,
Member of the European Parliament



Dear Friends

On behalf of the members of the European Gaucher Alliance I am pleased to bring you our publication of the proceedings of the 10th European Working Group on Gaucher Disease. Patients and their representatives do not underestimate the huge importance of this workshop and the real impact that the presentations and discussions have on their daily lives. This publication brings a brief summary of the talks as a record and an inspiration for further study.

Before the workshop, the EGA has held its biennial meeting attended by patient representatives from 35 different countries. The EGA meeting is an opportunity for members to come together to share their experiences, work on common issues, provide support to each other, engage with industry and to set our agenda for the future work. The participation of Patient representatives at the Workshop is an encouragement for our activities and provides a vital opportunity to meet and engage with the world's experts in Gaucher disease.

The members of the EGA remain ever grateful to the founders of the EWGGD for their initiative in encouraging patient representatives to participate in the EWGGD workshops. We express our special thanks to the EWGGD Chairman Prof. and local organizer Dr Nadia Belmatoug for supporting and facilitating with such generosity the participation of the EGA and for making us a 'Partner of the Congress' and allowing us to actively engage in its planning and programming.

For those who have not received a copy, our recently produced brochure detailing the history of the EGA, some of the steps we have so far taken, as well as our hopes and aspirations for the future, is available to download from our website www.eurogaucher.org. I do hope that you find it interesting. Notwithstanding the huge advances since the first EWGGD in Trieste in 1994 there remain unmet needs and new challenges are emerging. The coming together of the world's experts, drawing on their experiences and creativity to address these issues remains a source of excitement and gratitude for Gaucher patients.

Finally I thank Dr Efstathia Chronopoulou and Ms Juliane Arndt who had the task of writing up the presentations and preparing them for printing in this publication.

With warmest good wishes



Jeremy Manuel OBE
Chairman, European Gaucher Alliance

Directors
Yossi Cohen (Israel)
Tanya Collin-Histed (UK)
Anne-Grethe Lauridsen (Denmark)
Jeremy Manuel OBE (UK)
Pascal Niemeyer (Germany)
Johanna Parkkinen (Finland)
Radoslava Tomova (Bulgaria)
Sandra Zarina (Latvia)
Irena Žnidar (Slovenia)

Austria Belgium Bosnia & Herzegovina Bulgaria Czech Republic Denmark Estonia Finland France Germany Greece India
Ireland Israel Italy Jordan Latvia Lithuania Macedonia Mexico Netherlands Norway Poland Romania Russia Serbia
Slovakia Slovenia South Africa Spain Sweden Switzerland UK Ukraine USA

The European Gaucher Alliance Registered in England & Wales No. 6653373 Registered office: 340 West End Lane, London NW6 1LN, UK

Index of Presentations in order of delivery

- **A tribute to Joseph Tager: On the value of fundamental laboratory research: Novel chemical tools and methods to study Gaucher disease pathophysiology and therapies**
Prof Hans Aerts, Netherlands 11
- **Phenotypic spectrum of hematological and visceral disease in type 3 Gaucher disease: Genotype correlations and response to Imiglucerase therapy in 380 patients from the ICGG Gaucher Registry**
Prof Pramod Mistry, USA 12
- **Analysis of brains from a mouse model of neuronopathic Gaucher disease reveals progressive and localized pathology from birth**
Ahad Rahim, UK 12
- **The role of novel, non sphingolipid storage molecules in the pathogenesis of type 3 c Gaucher disease**
Jonathan Roos, UK 13
- **Cell surface associated glycohydrolases in normal and Gaucher disease fibroblasts**
Sandro Sonnino, Italy 13
- **Long-term follow up of the Mainz cohort of Gaucher disease type 3 patients**
Jörg Reinke, Germany 14
- **Presentation of EGA**
Jeremy Manuel, OBE, UK, Tanya Collin-Histed, UK, Pascal Niemeyer, Germany, Johanna Parkkinen, Finland, Radoslava Tomova, Bulgaria 14
- **Basis of immune dysregulation in Gaucher disease**
Ozlem Goker-Alpan, USA 15
- **Fatal B cell lymphoma in experimental Gaucher disease**
Elena Pavlova, UK 15
- **Severe impairment of regulatory T cells and other numerical peripheral blood T lymphocyte abnormalities in patients with Gaucher disease**
Sotiropoulos C, Symeonidis A, Greece 16
- **Multilineage dysplasia of bone marrow is a frequent phenomenon in untreated Gaucher disease type I**
Monika Klimkowska, Sweden 16
- **Preventing Lysosomal storage diseases by preimplantation genetic diagnosis**
Gheona Altarescu, Israel 17
- **Transient elastography (TE) of spleen (Fibrospleen) and liver (Fibroscan) in patients with splenomegaly: A pilot study**
Stephan vom Dahl, Germany 17
- **Is measurement of liver elasticity and liver iron content of value in patients with Gaucher disease?**
Laura Van Dussen, Netherlands 18
- **Fine needle aspiration versus trephine biopsy of bone-marrow – comparison of utility and diagnostics of sporadic cases of Gaucher disease type 1: A cytohistological study**
Maciej Machaczka, Sweden 18
- **Molecular profiling of Gaucher disease by Fourier transform infrared spectroscopy**
Serap Dokmeci, Turkey 19
- **Diagnosing Gaucher disease: An ongoing need for increased awareness amongst haematologists**
Derralynn Hughes, UK 19

(continued opposite)

- **Mesenteric and mediastinal lymphadenopathy in Egyptian children with Gaucher disease: A study of 6 patients. Can enzyme replacement therapy (ERT) play a role in improving their condition?**
Magy Abdelwahab, Egypt 20
- **Lecture on β -Glycosphingolipids as immune modulators for oral immune therapy**
Yaron Ilan, Israel 20
- **Long term bone mineral density response to enzyme replacement therapy in a retrospective paediatric cohort of Gaucher patients**
Dr Bruno Bembi, Italy 21
- **Glucocerebrosidase deficiency in zebra fish leads to primary osteogenic defects**
Enrico Moro, Italy 22
- **Glucocerebrosidase deficiency in mesenchymal stem cells from a cohort of 10 Gaucher disease type 1 patients leads to abnormal osteogenesis**
Nadia Belmatoug, France 22
- **Taliglucerase alfa leads to favourable bone marrow responses in patients with type 1 Gaucher disease**
Laura Van Dussen, Netherlands 23
- **Lecture on Pathophysiology of skeletal manifestations in type 1 Gaucher disease**
Pierre Lafforgue, France 23
- **Abnormal hemorheological and adhesion properties of red blood cells in Gaucher disease**
Cyril Mignot, Yves Colin-Aronovicz, France 24
- **Histological findings of femoral heads from patients with Gaucher disease treated with enzyme replacement**
Ehud Lebel, Israel 24
- **Bone parameters in adults with type 1 Gaucher disease treated with Velaglucerase alfa in trial TKT025 and the extension study: focus on the bone marrow burden scores over 7 years**
Deborah Elstein, Israel 25
- **Whole body MRI technique in early treated non-neuronopathic patients with enzyme replacement therapy at least eight years**
Eugen Mengel, Germany 25
- **Lecture: The nurse experience**
Liz Morris, UK 26
- **Lecture: The patient experience**
Wout Timmerman, Netherlands 26
- **The unique role of the clinical trial nurse**
Yehudit Chen Zion, Israel 27
- **Design of a therapeutic patient education for Gaucher disease patients: The French experience**
Christine Serratrice, France 27
- **Phase 2 multicenter, open label, switch over trial to evaluate the safety and efficacy of Abcertin (Imiglucerase) in patients with type 1 Gaucher disease previously treated with Imiglucerase**
Han wook Yoo, Korea 28
- **ZAGAL Study: Long-term management and follow-up of use of Miglustat in type 1 Gaucher disease in Spain**
Pilar Giraldo, Spain 28

(continued overleaf)

- **Eligustat, an investigational oral therapy for Gaucher disease type 1: Phase 2 results after 4 years of treatment**
Elena Lukina, Russia 29
- **Velaglucerase as therapy for Gaucher disease**
Deborah Elstein, Israel..... 29
- **Incidence of Parkinson disease in obligate carrier relatives of patients with Gaucher disease: A single center report**
Tama Dinur, Israel..... 30
- **Gaucher disease: From ERAD of mutant glucocerebrosidase variants to Parkinson disease**
Inna Bendikov-Bar, Israel..... 30
- **The E3 ligase itch regulates degradation of mutant glucocerebrosidase**
Gali Maor, Israel 31
- **Psychosines implicated in the pathogenesis of Gaucher disease alter actin dynamics and perturb intracellular lysosomal trafficking**
Jonathan Roos, UK..... 31
- **Competition law and Gaucher and other orphan drug pricing**
Hanna Hyry, Jonathan Roos, Timothy Cox, UK 32
- **Lecture: Investigation of a novel approach to treat patients with Gaucher disease**
Roscoe Brady, USA 32
- **Activation of the unfolded protein response in Gaucher disease**
Mia Horowitz, Israel..... 33
- **Exploring bicyclic derivatives of L-idonojirimycin as pharmacological chaperones for the treatment of Gaucher disease**
Pilar Alfonso, Spain 33
- **The pharmacological chaperone AT3375 alone and in combination with recombinant human acid β -Glucosidase for Gaucher disease**
Elfrida Benjamin, USA 34
- **Long-term clinical outcomes in type 1 Gaucher disease following 10 years of Imiglucerase treatment**
Stephan vom Dahl, Germany..... 34
- **Plant-cell-expressed recombinant glucocerebrosidase – Taliglucerase –alfa as therapy for Gaucher disease in patients previously treated with Imiglucerase**
Gregory Pastores, USA 35
- **A multicentre, double-blind, randomized safety and efficacy study of two dose levels of Taliglucerase-alfa in pediatric subjects with Gaucher disease**
Ari Zimran, Israel..... 35
- **The French Gaucher disease registry: Clinical characteristics, complications and treatment of 562 patients**
Nadia Belmatoug, France 36
- **Developing lentiviral vectors for gene therapy of type 1 Gaucher disease**
Katherine Aitchison, UK 36

Index by Speakers

Abdelwahab Magy 20	Lukina Elena 29
Aerts Hans..... 11	Machaczka Maciej..... 18
Aitchison Katherine 36	Manuel Jeremy 14
Alfonso Pilar 33	Maor Gali 31
Altarescu Gheona 17	Mengel Eugen 25
Belmatoug Nadia 22,36	Mignot Cyril 24
Bembi Bruno 21	Mistry Pramod..... 12
Bendikov-Bar Inna 30	Moro Enrico 22
Benjamin Elfrida 34	Morris Liz 26
Brady Roscoe..... 32	Niemeyer Pascal 14
Chen Zion Yehudit..... 27	Parkkinen Johanna 14
Colin-Aronovicz Yves 24	Pastores Gregory 35
Collin-Histed Tanya 14	Pavlova Elena 15
Cox Timothy 32	Rahim Ahad 12
Dinur Tama..... 30	Reinke Jörg..... 14
Dokmeci Serap 19	Roos Jonathan..... 13,31,32
Elstein Deborah..... 25, 29	Serratrice Christine 27
Giraldo Pilar 28	Sonnino Sandro..... 13
Goker-Alpan Ozlem 15	Sotiropoulos C..... 16
Horowitz Mia 33	Symeonidis A..... 16
Hughes Derralynn..... 19	Tomova Radoslava..... 14
Hyry Hanna 32	Timmerman Wout 26
Ilan Yaron 20	Van Dussen Laura..... 18,23
Klimkowska Monika 16	vom Dahl Stephan..... 17, 34
Lafforgue Pierre..... 23	Yoo Han wook..... 28
Lebel Ehud 24	Zimran Ari 35

Our Thanks Go To.....

The European Gaucher Alliance (EGA) are extremely grateful to Dr Efstathia Chronopoulou and Ms Juliane Arndt who attended the EWGGD in Paris as guests of the EGA to write the summaries in this supplement, so that our members, families, friends and those interested in Gaucher disease not able to attend this workshop could be kept up to date on what is happening in the field.



Efstathia Chronopoulou

Dr Efstathia Chronopoulou, from the UK, trained in the University of St Andrews where she obtained her BSc in Experimental Pathology followed by a medical degree in Cambridge University. Efstathia specialised in Paediatrics and recently completed her studies leading to the award of the Certificate of Completion of Higher Specialist Training in General Paediatrics and Paediatric Metabolic Medicine. She is currently pursuing a research degree in the field of paediatric metabolic medicine.



Dr Juliane Arndt

Ms Juliane Arndt, a medical student and doctoral candidate from Germany, enrolled at the Johannes Gutenberg University in Mainz in April 2009 and is now in her 8th semester. Since January 2012, Juliane has worked as a doctoral candidate and research assistant in the metabolic section at the University Clinic in Mainz with a focus on the phenotype of Gaucher Disease Type III.

SESSION 1: Opening Session

A tribute to Joseph Tager: On the value of fundamental laboratory research: Novel chemical tools and methods to study Gaucher disease pathophysiology and therapies

Prof Hans Aerts, Netherlands

Prof Aerts started his talk with a tribute to Joseph Tager, one of the founding fathers of EWGGD who peacefully passed away last year. His life and achievements were presented as well as his aspiration for the group to serve the need for independent and applied biomedical research in Gaucher disease.

Gaucher disease is the best understood lysosomal storage disorder with the primary biochemical defect being insufficient activity of the lysosomal acid β -glucosidase or glucocerebrosidase (GBA1). Deficiency of GBA1 in macrophages causes them to transform to the lipid-laden cells that are the hallmark of the disorder, while the consequences of this enzyme deficiency in other cell types are still poorly understood.

Satisfactory clinical responses are shown with treatment by means of chronic Enzyme Replacement Therapy (ERT). Small compounds are currently in development for Substrate Reduction Therapy (SRT) and Pharmacological Chaperone Therapy (PC).

Gaucher disease remains a topic of exciting basic and clinical field of research. Mouse models and novel technologies have boosted a new phase of fundamental research. Novel achievements in fundamental laboratory research were discussed.

The crystal structure of GBA1, visualised 5 years ago, has helped scientists to develop molecules called inhibodies. These are molecules that mimic the substrate and covalently bind to it. They are irreversible GBA1 inhibitors, such as conduritol β -epoxide. This has helped develop a simple and ultra-sensitive method of detecting GBA1 in cells, with such accuracy that enzyme activity in only one cell can be detected. More importantly, it is also possible to follow the fate of labelled GBA1 enzyme in cultured macrophages and mice using time-laps microscopy in living cells. In vivo labelling is crucial in showing tissue distribution of GBA1 activity. With this method, cerezyme and velaglucerase have been studied in cultured human macrophages. It is aimed to develop infra-red labelled inhibodies allowing to monitor the tissue targeting of therapeutic enzyme in patients. GBA2 activity, the non-lysosomal glucocerebrosidase has been implicated in the neuropathology of Niemann-Pick C disease. In this direction, another class of activity-based-probe (ABP) has been developed, called the anybody. This molecule promiscuously binds to all the glucosidases of the cell including GBA2, leading to toxic accumulation of ceramide in the cytosol.

In the on-going search for new biomarkers in Gaucher disease, gangliosides and glucosylsphingosine are being studied. Glucosylsphingosine is elevated in the blood of Gaucher disease patients and is a promising biomarker in development. There is accelerated accumulation with time of GBA1 inactivation.



Phenotypic spectrum of haematological and visceral disease in type 3 Gaucher disease: Genotype correlations and response to Imiglucerase therapy in 380 patients from the ICGG Gaucher Registry

Prof Pramod Mistry, USA

In this study 380 patients with type 3 Gaucher disease (GD) from the International Collaborative Gaucher Group (ICGG) were analyzed to see the long-term outcome of using imiglucerase as enzyme replacement therapy, the GBA genotype distribution and to define the spectrum of visceral and hematologic disease. Clinical parameters were assessed at initiation of therapy and followed for up to 5 years.

L444P and D409H were the most common mutations analyzed in patients and the majority were diagnosed and treated before the 6th year of life showing devastating conditions of visceral and hematological disease and growth retardation already in early childhood. Within the first year of therapy and furthermore in following years, these life threatening complications could be prevented. This was consistent with reduction of liver and spleen volume as well as higher hemoglobin, platelet count levels and bone mineral density. Among the 62 patients who died, the most frequent causes of death were: progressive neurological diseases followed by infection and cardiac complications. As a result therapy with imiglucerase can be seen as a noteworthy improvement for patients with GD3, a disorder associated with an increased mortality and life-threatening complications.



Analysis of brains from a mouse model of neuronopathic Gaucher disease reveals progressive and localized pathology from birth

Ahad Rahim, UK

The very rare Gaucher disease (GD) type II is characterized by rapid neurological progression resulting in death by 2 years of life. So far conventional medicine offers no therapeutic option due to the inability of enzyme replacement therapy to cross the blood brain barrier. To get an insight into the disease pathology, where substrate accumulation has already been reported at birth in patients and therapeutic opportunities are absolutely needed, Dr. Rahim investigated the brains from an acute mouse model of GDII that die at ~14 days after birth. Pathological analysis was conducted at the first day, 8th day and 12th day of life which was already close to death.

Until day 10 the body weight seems to be normal followed by a rapid decrease in the remaining days of life. Inflammation caused by microglia, resident macrophages of the central brain system responsible for the first immune defense, was evident at birth in the brain stem and extended to other areas of the brain as seen at day 8 and 12. A similar impression was given by the increase of astrocytes which are multifunctional cells in the brain with mainly supportive tasks. Progressive neuronal loss was revealed as well as a significant increase of apoptosis (programmed cell death) particular in the brain stem. Already at birth mitochondria, the "cellular power plants" showed an abnormal morphology and low membrane potential. The investigation of the one day old mice suggests that there are particular regions of the brain which are more susceptible to pathology than others narrowing the window for therapeutic options. Interestingly, rods and tangles of alpha-synuclein, a protein of particular interest to the Parkinson Disease community, were histologically detected as early as in 1 day after birth.

Although the investigations are shedding light upon the disease progression in GDII, the data is also likely to be useful in furthering our understanding of the less severe GDIII.



The role of novel, non sphingolipid storage molecules in the pathogenesis of type 3 c Gaucher disease

Jonathan Roos, UK

Type IIIc Gaucher disease (GDIIIc) is a rare form of Gauchers which is reminiscent of the Mucopolysaccharidosis disorders and affects the eyes, heart and brain. There is much calcification. The disease is caused by a unique mutation in the Gaucher enzyme called D409H. As Gaucher patients also store other substances which are not directly broken down by the Gaucher enzyme Dr Roos and Prof Cox investigated whether the enzyme might have undiscovered activities which could account for such storage. A number of alternative enzyme functions were found, such as acid beta xylosidase, however the activity was not affected by the GDIIIc mutation. Together with Dr Penny Stein, the team then examined the 3D structure of the enzyme to look for clues as to why GDIIIc is such an unusual disease. Dr Roos also studied the urine of patients and found that 1 patient had high oxalate levels- a substance associated with calcification of tissues. On testing two younger patients, their oxalate level was also found to be at the very upper limit of what is normal, and despite being much less affected by the disease. We still do not fully understand what causes the calcification in GDIIIc disease but the Cambridge team have opened up some new avenues for further research.



Cell surface associated glycohdrolases in normal and Gaucher disease fibroblasts

Sandro Sonnino, Italy

In Gaucher disease (GD) sphingolipid (SL) metabolic pathways are affected by dysfunction of the enzyme β -glucocerebrosidase (GluCer) present in intracellular fractions as well as in the plasma membrane. Many additional enzymes are involved in the SL metabolism which mainly takes place inside the lysosome but it was shown that enzymes which modify lipids were also associated with the plasma membrane and that enzymes regulate interactions between the glycosphingolipids and the proteins.

In this study activities of the lysosomal GluCer (GBA1) and the non-lysosomal GluCer (GBA2) were tested in plasma membranes of fibroblasts from GD patients and healthy controls and in total cell lysates. GBA1 activity was found to be low in all cohorts and investigated cells, but GBA2 activity was increased in GD cells and even different in between the three GD types. The high GBA2 enzyme activity was related with a higher expression of the GBA2 protein. Similar observations were made with other enzymes involved in SL catabolism, which leads to the suggestion of a cross-talk between the enzymes. This also may serves as a tool to improve the classification of GD phenotypes.



Long-term follow up of the Mainz cohort of Gaucher disease type 3 patients

Jörg Reinke, Germany

In this study 22 patients suffering from Gaucher disease type III were analysed by the modified Severity Scoring Tool (mSST) containing neurological features for an average of 8 years to gain insights into disease progression and phenotype-genotype correlations. It was possible to split the cohort into two groups: one "classical type" with no other mutations than L444P and D409H and the other "progressive type" with the occurrence of other mutations than in the first group. Main differences were seen in a higher yearly increase of the mSST score, severe and disabling motor dysfunction and the occurrence of neurological symptoms particularly saccadic dysfunction and bulbar signs before visceral ones in the progressive type. 8 patients developed epilepsy with mostly complex-focal seizures and secondary generalization at a wide range of ages. An adult onset was seen in 3 patients, all with epilepsy. Generally symptoms appeared between the first two years of life and the progression rate was predominantly low resulting in a meaningful benefit for patients from enzyme replacement therapy. As prognostic factors for bad outcome development of myoclonus, mutations others than L444P and D409H and splenectomy were found



Presentation of the European Gaucher Alliance (EGA) to the EWGGD

Jeremy Manuel, OBE, UK, Tanya Collin-Histed, UK, Pascal Niemeyer, Germany, Radoslava Tomova, Bulgaria and Johanna Parkkinen, Finland

JM introduced the European Gaucher Alliance, a company incorporated and registered in England. Its membership is made up of groups representing Gaucher patients from 35 national member associations.

The aims of the EGA are:

- To collect information on advances in the understanding, management and treatment of Gaucher disease and disseminate it to interested groups
- To provide information support guidance to groups throughout Europe
- To promote research
- To work with the medical and scientific community forum for ethical issues
- To ensure equality of treatment

The EGA presented to the EWGGD four different areas from their work programme which they chose to do under 4 different headings:

- 1) Looking back to go forward
- 2) Humanitarian Aid (Giving a Tomorrow)
- 3) Building tomorrow's leaders
- 4) Working to address the impact of the economic climate

From the reports of member associations it becomes evident that the Gaucher patient world is divided into 3 categories: (a) those who are able to receive treatment, (b) those with varying degrees of access to treatment and (c) those where no treatment is available.

TCH reported on the EGA's major activity of being instrumental in the establishment of Genzyme's European Enzyme Access Program (ECAP) which provided humanitarian



aid to Gaucher patients and has resulted in treating 120 patients from 30 countries, for whom treatment would not otherwise be available.

In October 2011, the EGA together with EWGGD and the National Gaucher Foundation (NGF) from the USA hosted a meeting of the 5 leading pharmaceutical companies to develop a pathway to establish a Global Humanitarian Program for Gaucher patients. One of the outcomes is to seek the establishment of pilot programmes for Humanitarian Aid in India and Pakistan.

Working together the EGA and the National Gaucher Foundation receive requests for help on a daily/weekly basis to access treatment on a humanitarian aid basis from physicians, patients and their families in countries where they are unable to access treatment through their own Government. The list of countries continues to grow and currently include; Morocco, Sudan, Pakistan, India, Portugal, Tunisia, Albania, Singapore, Kenya and Ukraine, Romania, Iraq and Jordan.

PN reported on the different communication channels available to the EGA's members as well as external parties interested in the disease. He gave a short update on the new website which enables patients and physician, as well as other interested people, to get general information about the disease and about its members, the local patient organisations. Furthermore the EGA has, for the first time, presented a poster at the EWGGD informing about its work programme and its aims and objectives. PN also gave an update on the internal communication with its members: the EGA now sends out regular newsletters including all kinds of information which could be of interest for the local organisations.

Basis of immune dysregulation in Gaucher disease

Ozlem Goker-Alpan, USA

There is clinical evidence of immune dysregulation in Gaucher disease.

The study presented in this talk explored this further by immune profiling 14 patients, the majority of Ashkenazi Jewish origin with more females than males. CD14+ monocytes, CD4+lymphoid dendritic cells and CD1d-restricted NK cells were greatly reduced in patients. Natural killer cells were greatly reduced but displayed a more activated/differentiated phenotype. There was also a profound decrease in naive T lymphocytes. The B cells showed hyper proliferation and a shift to more mature cells.

In conclusion, the study showed highly significant and profound differences in immunoprofiling results between subjects with Gaucher disease and controls. These profiles correlated with disease severity but also response to therapy, opening the way for their potential future development to be used as disease biomarkers.

Fatal B cell lymphoma in experimental Gaucher disease

Elena Pavlova, UK

Dr Pavlova from Cambridge presented interesting research into the development of multiple myeloma and B cell lymphoma in Gaucher disease.

Mice with inducible GBA1 deficiency in the haemopoietic cells were mated and offspring received parenteral inducer, providing a GD mouse model and a matched control according to their genetic constitution.

Several, GD mice had lost more than 20% of their adult body mass and obvious tumours were seen in the mesenteric tissues at post mortem. The tumours stained positive for B cell lymphomas. Glycosphingolipids were measured in tissues and in plasma. Glucosylsphingosine was raised in plasma while β -glucosylceramide was elevated in liver and spleen tissue.

This strain of inducible GD mice has an increased frequency of age-dependent lethal B cell malignancies and can serve as a model to investigate the role of sphingolipids in B cell proliferation and human lymphoid cancer pathogenesis in Gaucher disease



Severe impairment of regulatory T cells and other numerical peripheral blood T lymphocyte abnormalities in patients with Gaucher disease

Sotiropoulos C, Symeonidis A, Greece

Dr Symeonidis presented very interesting data from Greece.

A cohort of 25 patients with GD type I were studied. Median age was 41 years (1 <10 years). 6 patients were splenectomized. 20 were on ERT, 2 on SRT, 3 not on any treatment and one patient was treatment naive. Peripheral blood was analysed using 4-colour whole blood flow cytometry to distinguish the various lymphocyte subpopulations.

They showed significant numerical impairment of the total lymphocyte count, total T-lymphocytes and T-helper lymphocytes, including memory and naive CD4 cells. Although GD patients exhibited increased proportions of activated, both, CD4 and CD8 lymphocytes, their regulatory T-cell compartment was impaired, and this was associated with loss of efficient suppressor function and overwhelming T-cell activation. They also showed associated chronic B cell stimulation, but auto reactive B-cells were not increased. All NK cell populations were not significantly different between GD patients and controls.

These findings may explain the chronic inflammatory status and the increased incidence of lymphoid malignancies of patients with GD.



Multilineage dysplasia of bone marrow is a frequent phenomenon in untreated Gaucher disease type I

Monika Klimkowska, Sweden

Dr Klimkowska, from the Karolinska University hospital in Sweden, presented her work on the presence of dysplastic (pre-cancerous and cancerous) changes in the bone marrow of GD type 1 patients.

Myelodysplastic syndromes are malignant diseases with abnormal proliferation of a bone marrow stem cell progeny of clonal origin, i.e. all the cells have differentiated from one pluripotent progenitor parent cell.

Bone marrow specimens from 17 untreated patients with GD1 from Sweden, Lithuania and Poland were reassessed and analysed for dysplastic changes in 3 haemopoietic lineages (i.e. red blood cells, white blood cells and platelet progenitor cells) according to objective WHO criteria. Mean age was 56 years. 4 patients were splenectomised.

The study showed significant dysplasia in most GD1 patients even with a normal peripheral full blood count or after splenectomy.

Gaucher cell infiltrates were implicated in the pathogenesis as they may disturb the normal haemopoietic process either through cytokine production, interfering with local blood supply or local fibrosis of the bone marrow i.e. altering the microenvironment where normal haemopoiesis occurs.

The potential clonal nature of the observed abnormalities needs to be further investigated.

Preventing Lysosomal storage diseases by preimplantation genetic diagnosis

Gheona Altarescu, Israel

Dr. Altrasecu presented how preimplantation genetic diagnosis (PGD) can allow the birth of unaffected children for couples at risk from a genetic disorder. She also showed the strategy and outcome of its use in Gaucher disease (GD). The first PGD baby was born in 1989, from that time on PGD's use has found increasing application for many different single gene diseases with a known genetic base. PGD requires In Vitro Fertilization (IVF) with intracytoplasmic sperm injection (ICSI) which may increase the risk of birth defects. Eggs from the ovaries are taken and fertilized in the laboratory. During the first days of the embryos several diagnostic analyses of cells are made to ensure that no genetic defects are existent. For the investigation a special measurement is used which includes mutations occurring in the family and 6 additional markers for common pathologies. Afterwards the healthy embryo is injected into the uterus.

In 4 families with risk of the birth of a baby with GD PGD was used. One couple had the combination of Tay Sachs and Gaucher. All of them gave birth to a healthy child by the use of in mean 1,5 PGD cycles. The overall take home baby rate per family used PGD in several disease was 85% in their unit. As a conclusion PGD can be seen as a reliable alternative to pregnancy termination. In the future stem cell lines with naturally occurring mutations and the effect of neurodegeneration will be the focus of investigation.

Transient elastography (TE) of spleen (Fibrospleen) and liver (Fibroscan) in patients with splenomegaly: A pilot study

Stephan vom Dahl, Germany

Transient elastography (TE) is an ultrasound-like non-invasive technique used to determine the stiffness and degree of fibrosis in chronic hepatitis C and other chronic liver diseases. The use of TE to detect accurately fibrotic processes in the spleen was not evidence-based so far and therefore was a purpose of their study. Some Gaucher patients show splenomegaly, which is resistant to treatment and might be due to irreversible fibrosis. The aim of the examination of this trial was to see whether increased spleen stiffness generally occurs in splenomegalic patients and if there is a correlation between the size of liver, spleen and the stiffness.

Four groups of patients participated. One with Gaucher disease (GD) all under therapy, another with compensated liver cirrhosis and the third one with splenomegaly because of other diverse reasons. Results from these groups were compared to results of a control group without splenomegaly. It was found that the accuracy of liver elastography is higher than Fibrospleen probably caused by the smaller size of the spleen and its anatomical shape. Patients with compensated liver cirrhosis obtained the highest TE values in both groups. Size of spleen and stiffness were not clearly related and in neither liver nor spleen a statistically difference between TE values in Gaucher patients and the healthy controls were found. As they were not included in the small Gaucher-group in further studies GD patients with a resistant splenomegaly or low platelet count should be investigated by TE.



Is measurement of liver elasticity and liver iron content of value in patients with Gaucher disease?

Laura van Dussen, Netherlands

In Gaucher Disease (GD) liver-related complications like fibrosis and increased risk for developing a hepatocellular carcinoma can occur. Splenectomized GD patients might be particularly at risk. The metabolism of iron in GD is still under investigation. Elevated ferritin levels, also used as a disease marker, and iron accumulation in Gaucher cells have been described and may contribute to the pathogenesis of liver fibrosis. For the identification of at-risk patients, development of adequate diagnostic tools is needed. Therefore the potential usefulness of measuring liver fibrosis by Fibroscan and MR elastography (MRE) in relation to disease markers, parameters of iron metabolism and hepatic iron content as measured by MRI were evaluated in the study. Results of seven splenectomized GD patients, seven non-splenectomized GD patients and seven healthy volunteers were compared.

There was no difference in the liver iron content found between the groups and liver iron content did not correlate with fibrosis, but did correlate with ferritin levels. The results of MRE and Fibroscan measurements in non splenectomized patients did not differ significantly from the control group, but splenectomized GD patients showed elevated values for both these measures of fibrosis. MRE and Fibroscan might be useful to monitor elasticity and fibrosis of the liver in GD patients. Correlation between iron content and fibrosis should be investigated in larger groups



Fine needle aspiration versus trephine biopsy of bone-marrow – comparison of utility and diagnostics of sporadic cases of Gaucher disease type 1: A cytohistological study

Maciej Machaczka, Sweden

Generally bone marrow examination is not recommended for the definitive diagnosis of Gaucher disease (GD) but often initial symptoms like low platelets count (thrombocytopenia) or enlargement of spleen (splenomegaly) lead to haematological diagnostic work-up. In this case either fine needle aspiration (FNA) is used where semi liquid bone marrow is yielded and bone marrow smears (BM-S) are cytological assessed. Another diagnostic is done by bone marrow trephine biopsy (BM-TB) where a narrow solid piece of bone marrow is histologically examined under a microscope. So far little is known about the utility and accuracy of the two diagnostic forms in respect to GD. In this study six patients with GD were tested by both diagnostic forms to compare the results.

Dr. Machaczka and his colleagues were able to demonstrate that FNA is not a reliable diagnostic method for detecting Gaucher cells (GC) in bone marrow. In most patients among thousand cells, less than six GC were found. Thinking about the routine procedure where only two hundred cells are analysed the risk for not diagnosing GD is seriously high. This finding could be explained by the tightly packed GC, which are difficult to aspirate or by the fibrosis of bone marrow. In contrast the detected GC rate was about hundred times higher (in the same patient), when used BM-TB the proposed way of diagnostic in case of an unclear thrombocytopenia and splenomegaly. Moreover a negative BM-S does not exclude GD and routinely screening of enzymatic activity of β -glucosidase and chitotriosidase should be done.



Molecular profiling of Gaucher disease by Fourier transform infrared spectroscopy

Serap Dokmeci, Turkey

With Fourier transform infrared spectroscopy (FTIR) it is possible to study molecular diversity of samples and to determine the amount of particular compounds as well as the secondary structure of proteins in a fast and sensitive way. In this study FTIR was used to characterize biomolecules in Gaucher disease (GD) in comparison with a healthy control group. Protein and lipid levels were found to be increased whereas the bandwidth of stretching lipids was decreased, which indicates a decrease in membrane fluidity. Abnormal protein secondary structures were observed as well. Based on lipid spectograms the working group could find a classification of within the Gaucher Patients into moderate and severe. So FTIR may be a method with prognostic value in patients with GD.



Diagnosing Gaucher disease: An on-going need for increased awareness amongst haematologists

Derralynn Hughes, UK

Dr Hughes from the Royal Free Hospital in London, discussed the need for increasing awareness for GD amongst haematologists, as they are often the first specialist doctors a new Gaucher disease patient is referred to by the GP with bruising or splenomegaly.

She presented data on diagnostic delays in Gaucher disease in our era of specialist services and availability of treatment. The medical histories of Gaucher patients attending the Royal Free Lysosomal Storage Disorder Unit were reviewed and data collected on the time from symptoms to diagnosis, modality of diagnosis and diagnosing specialty.

Interestingly, median time to diagnosis is as long as 2 years, however, this reflects an improvement in recent years. The commonest diagnostic test is a bone marrow biopsy which goes hand in hand with the commonest diagnosing specialty being haematology. Enzyme assays were performed for confirmation of the diagnosis and not as the initial diagnostic test despite their availability over 4 decades.

Increasing awareness of Gaucher disease as a differential diagnosis for splenomegaly and cytopenias amongst haematologists could shorten the diagnostic course and reduce the need for invasive tissue biopsies.

After lively discussion, the plan is to request inclusion of Gaucher disease as a differential diagnosis in the UK national guidelines for investigation of low platelets.



Mesenteric and mediastinal lymphadenopathy in Egyptian children with Gaucher disease: A study of 6 patients. Can enzyme replacement therapy (ERT) play a role in improving their condition?

Magy Abdelwahab, Egypt

Dr Magy Abdelwahab from Cairo University Paediatric hospital, presented the rare finding of mesenteric and mediastinal lymphadenopathy in 6 Egyptian children with Gaucher disease. Gaucher disease was diagnosed on the basis of decreased leukocyte β -glucocerebrosidase activity and confirmed genetically with full sequencing of the gene.

Imiglucerase was given at 60IU/kg every 2 weeks to all patients at the start of treatment. There were 3 males and 3 females from 4 families. 3 had GD1 and 3 had GD3. 4 were symptomatic and 2 diagnosed on routine screening. All had a CT-guided biopsy of the mass. 3 patients had a stationary course, 1 showed regression of the mass upon increasing dose of ERT and 2 were newly diagnosed. None required surgical resection of the mass.

A lively discussion followed the talk trying to answer the following raised questions:

- Are mediastinal/mesenteric lymphadenopathy age, gender and Gaucher disease type related?
- What should be the diagnostic work-up and management protocol?
- What is the chance of the mass turning into malignancy?
- Is it related to the disease or to treatment with ERT?



β -Glycosphingolipids as immune modulators for oral immune therapy

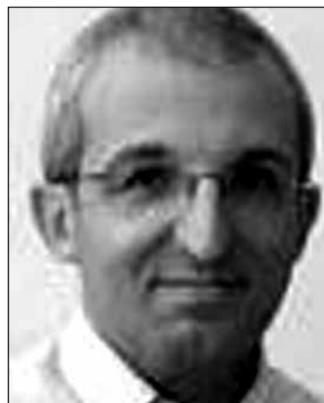
Ilan Yaron, Israel

Dr Ilan Yaron gave us a fascinating talk on immune modulation as a novel treatment approach using beta glycosphingolipids.

Immune modulation therapy is a novel approach in the treatment of autoimmune, infectious, malignant and inflammatory disease.

The gut mucosal immune system is the largest lymphoid organ in the body. This site has continuous antigenic challenges from food antigens, antigens of the abundant normal bacterial flora, and pathogens. Despite this constant antigenic stimulation, controlled inflammatory responses and suppression of inflammation appear to be the rule. The gut immune system differentiates the antigenic signals from the high background noise of food and bacterial antigens. This tight regulation required to maintain homeostasis is achieved through multiple non-immune and immune factors.

Oral tolerance is a mechanism in which the gastrointestinal immune system inhibits or promotes its reaction toward an orally administered antigen. Mucosal tolerance is attractive as an approach to the treatment of autoimmune and inflammatory diseases; the benefits of using an oral tolerance approach are: lack of toxicity, ease of administration over time, and antigen-specific mechanisms of action. Multiple mechanisms of tolerance are induced by oral antigen administration. Recent data suggest that oral antigen administration of antigens may promote



activation of different types of regulatory T lymphocytes, enabling treatment of immune mediated disorders.

The antigen/antibody complex is presented to the gut-associated lymphoid tissue (GALT). Regulatory T lymphocytes (Tregs) are specialized for immune suppression and are important regulators of the immune response in various settings. Tregs actively suppress enteroantigen-reactive cells and contribute to the maintenance of intestinal immune homeostasis. Distinct Treg subsets coexist in the intestinal mucosa and mesenteric lymph nodes. Disturbances in Treg number and function are associated with immune-mediated disorders. Therefore, Tregs are potential targets for immunotherapies.

β -Glycosphingolipids have emerged as a family of potential ligands for natural killer T (NKT)-regulatory lymphocytes. This subset of regulatory lymphocytes has been implicated in the regulation of autoimmune processes. The major histocompatibility complex (MHC) Class I-like CD1d glycoprotein is a member of the CD1 family of antigen-presenting molecules and is responsible for selection of NKT cells. β -Glycolipids have been shown to alter immune responses in the opposing settings of animal models of autoimmune diseases or cancer. Administration of GC inhibits NKT cell proliferation and alleviates the effects of ConA-induced hepatitis. It has also been shown to alleviate colitis and suppresses hepatocellular carcinoma growth.

Oral GC has also been studied in the metabolic syndrome. Obesity is now thought to be characterised by chronic activation of inflammatory pathways. Leptin-deficient ob/ob mice are overweight, develop insulin resistance, and serve as a model for type 2 diabetes. Dr Yaron's group investigated whether the induction of regulatory T cells could alleviate the pathological and metabolic abnormalities in ob/ob mice. They induced TGF- β -dependent CD4(+) latency-associated peptide (LAP)-positive Tregs by oral administration of anti-CD3 antibody plus beta-glucosylceramide. They found a decrease in pancreatic islet cell hyperplasia, fat accumulation in the liver, and inflammation in adipose tissue, accompanied by lower blood glucose and liver enzymes.

Can GC alter the structure of lipid raft and influence intracellular signalling? Can GC serve as an adjuvant in the gut immune system? Orally administered anti-CD3 and GC affects both the innate and adaptive immunity arms of the immune system. It skews the immune profile and has an immune modulatory beneficial effect. Promising data from the first Phase 1 clinical trial of anti-CD3 and GC (OKT3 and GC) as proof of concept were presented.

Alterations to intestinal micro biota seem to play important roles in the induction and promotion of liver damage progression and in the development and severity of NASH. Bacterial overgrowth, immune dysfunction, alteration of the luminal factors, and altered intestinal permeability are all involved in the pathogenesis of NASH and its complications, including progression to cirrhosis. A better understanding of the cell-specific recognition and intracellular signaling events involved in sensing gut-derived microbes will help in the development of means to achieve an optimal balance in the gut-liver axis and ameliorate liver diseases. The data presented support the notion that bacterial translocation may serve as a new therapeutic target for NASH. Bacterial translocation induces an immune imbalance leading to a state of chronic inflammation, fat accumulation in the liver, mitochondrial dysfunction and NASH.

Long term bone mineral density response to enzyme replacement therapy in a retrospective paediatric cohort of Gaucher patients

Dr Bruno Bembi, Italy

Dr Bruno Bembi from Italy presented interesting data on bone disease in paediatric Gaucher patients. About 80% of type 1 Gaucher patients have bone pathology and there is lack of correlation between bone and haematological/visceral involvement. Vascular alterations, increased intraosseous pressure and cytokine release are the main factors implicated in the pathogenesis of Gaucher bone disease.

He discussed the results of a study aimed to analyse the bone clinical history of a group of 18 patients who begun ERT during paediatric age and reached adulthood. Mean ERT follow-up was 11, 3 (range 4-17)

They received biweekly infusions of 20-60IU/kg of alglucerase/imiglucerase: nine patients started ERT in infancy and 9 patients started ERT during puberty. Fifteen patients showed normal Z-scores (Z-score \geq -2), 1 had an abnormal Z-score which normalized in adulthood.



(splenectomised siblings) had abnormal Z-scores which remained in the pathologic range during the entire follow-up. In the infancy treated group, the Z-scores were overall higher at baseline and improved during treatment, but they showed a significant decrease in puberty. In the puberty treated group, the Z-scores were overall lower at baseline but showed continuous improvement with treatment.

The following conclusions were therefore drawn from the data:

- Pubertal growth causes a decrease in bone mineral density;
- ERT normalises bone mineral density and growth;
- ERT precocity correlates with a better outcome;
- Persistence of disease activity may affect normal bone mineralization during puberty.

Glucocerebrosidase deficiency in zebra fish leads to primary osteogenic defects

Enrico Moro, Italy

Dr Enrico Moro from Italy presented exciting basic research on the pathogenesis of bone defects occurring in a fish model for the Gaucher disease.

The zebrafish glucocerebrosidase (GBA) protein shares a high degree of identity at the amino acid level with the human enzyme, suggesting a conserved function during evolution. GBA loss of function during the early stages of zebrafish development can be studied through the use of antisense morpholino-mediated knockdown which determine a 50% reduction in GBA protein translation. GBA morphants, i.e. fish embryos microinjected with morpholinos, display reduced bone mineralisation during early developmental stages, proving that the enzyme affects early bone formation. Candidate genes implicated in bone genesis show specific down regulation in zebrafish larvae lacking complete GBA activity. This aspect was studied by sophisticated molecular techniques that pinpoint a specific signalling pathway affected by GBA loss of function.

This basic research suggested that zebrafish can be used as an alternative suitable model to dissect bone pathogenetic events occurring in Gaucher disease. GBA loss of function causes early cellular and molecular alterations beyond the simple accumulation of undegraded material, which are tightly related to premature primary bone defects. These results raise the clinical concern as to whether novel early therapeutic therapies should be considered to better manage the skeletal disease in GD children.



Glucocerebrosidase deficiency in mesenchymal stem cells from a cohort of 10 Gaucher disease type 1 patients leads to abnormal osteogenesis

Nadia Belmatoug, France

Dr Nadia Belmatoug presented the data on osteogenesis from GD patients' bone marrow mesenchymal stem cells.

Bone marrow mesenchymal stem cells (MSCs) must be involved in bone and blood disease in GD as they represent multipotent progenitor cells i.e. they are the early ancestors of bone cells and support haemopoiesis.

Bone marrow MSCs were studied from GD type 1 patients regarding their capacity to differentiate into osteoblasts as well as their supportive role in haemopoiesis. GD type 1 MSCs show decreased proliferation and morphological abnormalities. They also show lower supportive capacity for haemopoiesis.

The data support the role of MSCs as key components of the bone marrow microenvironment in which haemopoiesis normally takes place.



Taliglucerase alfa leads to favourable bone marrow responses in patients with type 1 Gaucher disease

Laura Van Dussen, Netherlands

Taliglucerase alfa is a carrot-cell expressed recombinant β -glucocerebrosidase for the treatment of Gaucher disease.

Lumbar spine fat fraction is a measure of Gaucher cell presence in the bone marrow. Regarding the Ff measurements, these are lower in GD patients and increase upon effective treatment. An Ff of less than 23% is associated with bone complications. An increase of lumbar spine fat fraction indicates clearance of Gaucher cells from the bone marrow.

The data of the bone marrow fat fraction (Ff) measured during a double-blinded randomised phase III clinical study and its extension was presented.

4 patients were treated with 30IU/kg biweekly and 4 patients were treated with 60IU/kg biweekly. Results were compared with 15 untreated patients from the Dutch Gaucher database. Ff increased significantly in patients treated with Taliglucerase alfa compared to baseline and compared to untreated patients. The difference between the patient and control groups was already shown to be statistically significant after 12 months of treatment. There was no influence of antibodies to Taliglucerase alfa on response parameters. All other disease parameters also showed sustained improvement.



Invited lecture: Pathophysiology of skeletal manifestations in type 1 Gaucher disease

Pierre Lafforgue, France

Skeletal manifestations are the main cause of pain and disability in type 1 Gaucher disease (GD) but most events – not all - may be reversible by consequent therapy.

The pathogenesis and mechanism of bone deformities like Erlenmeyer flask occurring in the femur still remains hypothetical. Its high prevalence is not only specific for GD and does not bring clinical consequences. Bone necrosis is also a frequent complication and appears either as bone infarcts which can cause acute painful bone crises anywhere in the skeleton or be asymptomatic or as epiphyseal chronic osteonecrosis. This mainly affects femoral heads and often results in joint destruction and in the end prosthetic surgery. Unlike ostéonécroses secondary to other conditions, ostéonécroses in GD do not occur simultaneously but successively at any time and in any place of the skeleton. The mechanism behind the cell death is a restriction of blood supply to the bone which could be caused by blood vessel lesions as reported in one study, by vascular occlusion, possibly by lipid particles, or by compression of the vessels from outside. Indeed bone marrow enlargement found in GD might affect vasculature inside the bone. There are no well-established risk factors for osteonecrosis but this complication occurs more frequently in patients with a younger age at diagnosis of GD, those presenting with other skeletal manifestations and in splenectomized patients. The incidence of bone crisis can be decreased but not totally prevented by enzyme replacement therapy (ERT). Further, less frequent complications are fragility fractures of the vertebral bodies or the long bones. In the spine low bone mineral density, occurring in GD, is the main reason for vertebral fracture whereas the limbs fractures are promoted by osteolytic lesions. In conclusion the mechanisms of skeletal manifestations in GD are largely unknown but clearly driven by medullary infiltration by Gaucher cells. ERT can reduce pain, the occurrence of bone crisis, improve bone mineral density, and growth in the children, it also seems to reduce the risk of new osteonecroses. However, existing lesions, especially osteonecroses will not be affected by ERT and will need specific modalities, such as prosthetic joint replacement.



Abnormal hemorheological and adhesion properties of red blood cells in Gaucher disease

Cyril Mignot, Yves Colin-Aronovicz, France

Assuming that the underlying mechanisms of complications in Gaucher disease (GD), like osteonecrosis, can be connected with abnormal red blood cell (RBC) properties, this study focused on RBC morphology, adhesion and flowing characteristics in non-treated Gaucher patients (NTGD) as compared with healthy controls.

It was detected that 3% of the patients develop abnormal shaped RBC. Hemorheological studies showed reduced deformability and increased aggregation of RBC. GD RBC adhesion to endothelial cells and laminin alpha5, a major component of the extracellular matrix, was demonstrated to be enhanced. Expression and phosphorylation of Lu/BCAM, the only laminin receptor of erythroid cells, were increased in NTGD RBC. In patients with sickle cell anemia, similarities in the modus of adhesion occur. In further studies the normalization of the RBC abnormal properties in GD will be content of investigation.



Histological findings of femoral heads from patients with Gaucher disease treated with enzyme replacement

Ehud Lebel, Israel

Osteonecrosis is a frequent reported issue in Gaucher disease (GD) with the consequence of joint destruction and negatively affected quality of life. Aim of the examination of histology of surgically removed femoral heads was to assess the influence of enzyme replacement therapy (ERT) on bones and its infiltration with Gaucher Cells (GC) and to help in the decision whether and when replacement hip is needed.

26 specimens from of 22 patients were analyzed. 16 patients received ERT and 17 were splenectomized. Osteoarthritic change was evident in all cartilage specimens and in seven specimens no remnants of necrotic bone was found. GC infiltration was seen in 20% to 95% of the material and wasn't related with age, type of mutation or liver status of the patient but a trend was seen that a longer duration of ERT goes with a lower percentage of infiltration. For bone regeneration qualifiers a new scoring system containing osteoplastic rimming, presence of remodelling lines and new bone apposition was used but no correlations were found. All in all histological signs were not correlated with ERT duration or severity of GD and no justification is given to postpone surgical intervention.



Bone parameters in adults with type 1 Gaucher disease treated with Velaglugerace alfa in trial TKT025 and the extension study: focus on the bone marrow burden scores over 7 years

Deborah Elstein, Israel

In this Study initially 12 naïve Gaucher disease (GD) Type I patients received Velaglugerace alfa as enzyme replacement therapy for 9 months. Afterwards extension of the study was possible where the dose of enzyme was reduced stepwise from 60 to 30 Units per Kilogram per infusion. 10 patients completed at least 79 months. Besides hematologic and visceral parameters the focus of the study was on bone parameters observed by magnetic resonance imaging (MRI). Several scores were used to evaluate the bone marrow involvement (bone marrow burden score, BMB) and the bone mineral density (BMD, Z-scores and T-scores) of the lumbar spine and the femoral neck.

After 9 and 48 months statistically significant improvements were seen in hemoglobin levels and platelet counts and reduction of liver and spleen volumes. All patients had clinically significant bone involvement at baseline. By 24 and/or 36 months, there was statistically improved BMD Z-scores in nearly all patients as well as improved WHO categories of T-scores (from osteoporosis to osteopenia and from osteopenia to normal range) at both lumbar spine and the femoral neck. All patients showed meaningful improvements from baseline in the BMB scores (reduction by 2 points) during the first 9 month and continuously during the following years with all but one patient achieving normal range (0-1 point) at the lumbar spine. After 5 years no deterioration was seen. This improvement in bone pathology was independent of continuous high-dose therapy.



Whole body MRI technique in early treated non-neuronopathic patients with enzyme replacement therapy at least eight years

Eugen Mengel, Germany

The cohort with early GD manifestation and a high risk for progressive bone disease presented in this study had a long tradition as already reported at the 3rd EWGGD in Lemnos thirteen years ago. In the meantime the 14 patients have been under permanent monitoring especially the bone marrow response to enzyme replacement therapy (ERT) was in focus of examinations by Whole Body MRI. Therefore four different scores were used. All patients were under treatment before the age of ten. ERT was initiated with a dosage of fifteen to sixty units per kilogram. Maintenance dose was adapted to response to therapy, clinical symptoms and chitotriosidase, mean about 36 U/kg SD +/- 5 U/kg.

In this cohort the early beginning with ERT could prevent bone complications. In fact no patient showed joint destruction, growth retardation, osteopenia, fractures, bone infarct or even bone pain. Hematological and visceral complications occurred neither so the typical manifestations of GD were reduced to a minimum. Only the Vertebra disc ratio remained unimproved which may reflect the postponed fat conversion in "adult" bone marrow and should be followed in further studies.



Invited Lecture: The nurse experience

Liz Morris, UK

In her presentation Liz Morris provided an overview of the history of nursing from the beginning of the 19th century up to the complex requirements faced by nurses nowadays. In addition to clinical care they provide emotional support and have an educational mission towards patients who can in cases of chronic disease become key decision makers in their treatment process. Often nurses are a bridge between doctors and patients and help to translate the medical terminology into understandable language which has a beneficial effect on compliance. The role of nurses in research and, what is mainly appreciated by patients, in the management of clinical processes is becoming ever more important. For patients with extremely rare disease like Gaucher disease (GD) nurses are a crucial navigator for patients through the complex healthcare system from first diagnosis to expert patients.



Home care has, for about 20 years, been a step for patients into more independence. There are 3 different ways of home therapy in Europe. In Germany a small number of patients are trained by the hospital, they collect the enzyme there and then afterwards are completely independent. The second scheme is a community managed one with a partnership between hospital and community like in the Netherlands where 44 out of 64 patients receive ERT in this way. Training takes place in the hospital and then the local communities provide the enzyme and nursing support at patients' homes. In the UK, Israel and Switzerland there is system of house service provision where a home care company is able to provide patient training, all the needed material, the enzyme therapy and makes the nurse available for many options from complete dependence to independence according to the wishes and abilities of the patients. In the UK from 131 patients 116 are treated at home and in the last 20 years only very few allergic reactions appeared.

Invited Lecture: The patient experience

Wout Timmerman, Netherlands

Wout Timmerman was diagnosed with Gaucher disease at the age of nineteen. Now after twenty years he shares his experience as a patient in the Netherlands. In 1992 enzyme replacement therapy was introduced. With the help of doctors, nurses and especially with adaption of behaviour to his chronic disease he lives as normal as possible and accepted his life as a challenge. Above all independent self-medication helped to gain self-confidence and improve his quality of life by doing his own treatment at home. Through this he is self-sufficient and is responsible for his own situation. The major aim that all patients should get treatment at home was implemented by learning to prepare infusion, learning to inject yourself. Importantly is the need for good guidance of healthcare personal, because the insertion of needles causes stress and is often associated with anxious feelings. He made good experiences and learned to live with stress and his disease and also was able to gain self-confidence and discover new possibilities. He also points out his experience that compliance with Gaucher disease for patients has never been a problem. In particular he appreciates his experience with his doctor patient relationship which is characterized by guidance and also active involvement on an equal base. All those factors helped to improve health and to make the right decisions for him. He cherishes the privilege to get a treatment like this.



The unique role of the clinical trial nurse

Yehudit Chen Zion, Israel

A new evolving professional field in modern healthcare systems addresses the ensurance of safety and compliance of study participants as well as ethical considerations and patients well-being. The clinical trials nurse (CTN) with their nursing principles and differentiated clinical and critical thinking, interpersonal skills, bedside experience, patient advocacy, scientific knowledge, and understanding of individual behaviour are of great value in a research team as well as for patient outcome. With multiple tasks a large responsibility is held by CTN e.g. by enlisting, receiving informed consent, giving treatments (intravenous), ongoing maintenance, data collection, patient retention in the trial and data recording and follow up. Thereby a CTN not only improves quality of communication or adherence to protocol and increases recruitment of patients but also are in a most favorable role to promote patients' awareness for the necessity of clinical trials in advancement for their own health and successive improvement of quality of life.



Design of a therapeutic patient education for Gaucher disease patients: The French experience

Christine Serratrice, France

The CETG (Comité d'Evaluation du Traitement de la maladie de Gaucher) is about to design a Therapeutic Patient Education program for Gaucher disease patients in France as a part of chronic disease care program. The aim of this program is to increase the quality of life and enhance autonomy in health related decisions for patients by keeping them better informed. Problems which they have to face are the rarity of the disease and the highly polymorphic outcome.

As the first step patients needs are self-evaluated. In addition an interview with a professional/expert occurs to design the content of the program:

1st: A personalized consultation takes place to assess the patients' expectations and organize his/her educational training

2nd: Three educational group sessions with focus on the understanding of the disease, the everyday life including problems like fatigue and pain management and the appropriation the treatment of choice.

The last point is a follow up consultation, support and evaluation of patient's progress.

In autumn of this year the program will be submitted to the agency for agreement and is due to start in January 2013



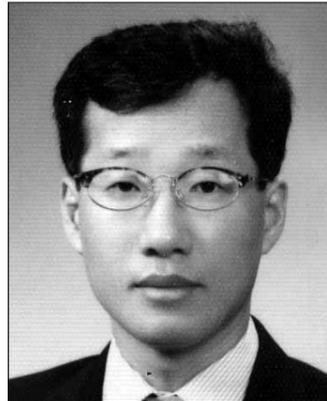
Phase 2 multicenter, open label, switch over trial to evaluate the safety and efficacy of Abcertin (Imiglucerase) in patients with type 1 Gaucher disease previously treated with Imiglucerase

Han wook Yoo, Korea

Dr Han wook Yoo presented data from Korea on this switch over clinical trial with a primary objective to evaluate the safety, tolerability and pharmacokinetics of Abcertin.

5 Korean patients, previously on treatment with cerezyme at 15-60IU/kg biweekly, were enrolled. Abcertin was started at the same dose. No adverse effects were observed. No clinically significant changes in haemoglobin, platelets, liver and spleen volumes, skeletal status and bone mineral density were found during the study period of 24 weeks. No antibodies to the drug were generated. This study showed a good safety, efficacy and tolerability profile of the drug in Gaucher disease type 1 patients already on treatment with cerezyme. Abcertin received approval by the Korean FDA.

Another clinical trial is under way to verify safety and efficacy of Abcertin in naive type 1 Gaucher disease patients.



ZAGAL Study: Long-term management and follow-up of use of Miglustat in type 1 Gaucher disease in Spain

Pilar Giraldo, Spain

Dr Pilar Giraldo showed us interesting data from Spain.

The study commenced in 2004 when approval for Miglustat in the EU was given.

Mild to moderate disease type 1 Gaucher disease patients, not on ERT were included. Some of these patients were treatment naive and some were previously treated with ERT. A total of 42 patients were treated with Miglustat (15 patients were treated for more than 7 years). In all of them the therapeutic goals were achieved. 14 patients reported gastrointestinal disturbances.

The study concluded that long-term treatment with Miglustat achieves and/or maintains therapeutic goals in mild to moderate Gaucher disease type 1 patients.

Overall tolerability is good. Individual variability in side effect profile was shown to be associated with dietary habits.



Eliglustat, an investigational oral therapy for Gaucher disease type 1: Phase 2 results after 4 years of treatment

Elena Lukina, Department of Rare Diseases, Haematology Research Center, Moscow, Russia

In Gaucher disease (GD), a deficiency of acid β -glucosidase activity results in glucosylceramide accumulation mainly in tissue macrophages, leading to the various clinical manifestations of the disease. The typical storage cells are called Gaucher cells. This Phase 2 international multicenter study investigates the long-term efficacy and safety of Eliglustat, an oral drug specifically working on the reduction of the substrate glucosylceramide.

In this study 26 adult GD type I patients, who had not been on any treatment for the last 12 months before participation in the clinical trial, were examined on several clinical criteria for 4 years under treatment with Eliglustat. At the end of this 4 year period, patients showed an increase in mean hemoglobin level of 2.3 g/dL and mean platelet count of 95%, and a decrease in mean liver and spleen volume of 28% and 63% respectively, compared to baseline. All patients met at least 3 of 4 long-term therapeutic goals. Improvement was also seen in the bone mineral density with the greatest benefit in patients with osteoporosis at baseline. Infiltration with Gaucher cells reflected in femur dark marrow was reduced or stable in 17 out of 18 patients. Eliglustat was well tolerated. Most adverse events were mild and not related to treatment. No new serious adverse events were reported in any patient between 3 and 4 years of treatment.

In 2013 data from a comparative phase III trial between Eliglustat and ERT will be available.



Velaglucerase as therapy for Gaucher disease

Deborah Elstein, Israel

Dr. Elstein first gave an introduction elucidating the difference between velaglucerase and other drugs used in enzyme replacement therapy (ERT) for Gaucher disease (GD). Potential advantages are the wild-type sequence and human cell line (proprietary) production system. The seminal Phase I/II trial met all its primary and secondary endpoints for anemia, thrombocytopenia and organ reduction as well as exploratory tertiary endpoints of improved bone mineral density and bone marrow burden score. There were further improvements during the extension despite a step-wise dose reduction (from 60 to 30 units/kg body weight/infusion) up to 7 years during which time therapeutic goals for these parameters were achieved earlier than expected. The safety profile of velaglucerase alfa was good with no hypersensitivity reactions and no patient developed antibodies to the drug. All potentially drug-related adverse events were mild to moderate and transient. Phase III trials included 2-dose comparisons (45 and 60 units/kg body weight/infusion, switch-over from imiglucerase to velaglucerase alfa (at the same dose), and a comparison to imiglucerase at the same dose (60 units/kg body weight/infusion). Taken together, the experience with velaglucerase alfa highlighted that a response in all analyzed clinical criteria was found and therapeutic goals were reached early and maintained. Switching from imiglucerase to velaglucerase alfa seems to be well tolerated: no patient developed antibodies against the enzyme even if there were antibodies against imiglucerase.



Incidence of Parkinson disease in obligate carrier relatives of patients with Gaucher disease: A single-center report

Tama Dinur, Israel

Dr Tama Dinur presented interesting data from Israel looking into the incidence of Parkinson disease among obligate carrier relatives of patients with Gaucher disease. 153 Gaucher disease patients (with 306 obligate carrier relatives) were interviewed within 8 months. Mean age was 66.4 years and sex distribution was equal.

The results show that 5.2% obligate carriers of Gaucher disease had Parkinson disease with a mean age of onset of 58.9 years.

This represents the first report of Parkinson disease incidence in carriers of Gaucher disease. The data implicate (1) higher incidence of Parkinson in carriers than patients (5.2% vs 2.4%, 12/510 patients in this clinic); (2) a later age of onset of Parkinson disease in carriers than Gaucher disease patients; (3) high prevalence of the N3705 mutation; and (4) equal sex incidence among obligate carriers.



Gaucher disease: From ERAD of mutant glucocerebrosidase variants to Parkinson disease

Inna Bendikov-Bar, Israel

Dr Inna Bendikov-Bar presented her research from Israel. Gaucher mutations have been identified as a major cause for Parkinson disease. The researchers tried to elucidate the relationship between the two. Mutant GCCase variants present variable degrees of ER retention and undergo ER associated degradation (ERAD) in the proteasome. ERAD requires specific E3 ligases which mediate ubiquitination of the wrongly folded protein. PARK2 is a gene implicated in Parkinson disease. It encodes the E3 ligase called Parkin. Parkin may be an E3 ligase for the mutant GCCase. Over expression of Parkin in Gaucher disease fibroblasts leads to a decrease in GCCase mutant variants. The hypothesis is that if Parkin is busy dealing with mutant GCCase variants, there is reduced degradation of natural Parkin substrates and subsequent cell death. One pathway includes PARIS which is a Parkin substrate. PARIS is a transcription repressor and is degraded in the proteasome via Parkin. If it is not broken down, it accumulates in the nucleus and down regulates expression of cell variability genes. The pro-apoptotic protein, Apoptosis Related protein in TGF β Signalling pathway (ARTS), is another substrate for Parkin.

In cells expressing mutant GCCase there is more cleavage of caspases 9 and 3 which is a hallmark of apoptosis. In cell viability assays, these cells are more susceptible to apoptotic stimuli, therefore they are less able to cope with stress.

The hypothesis is that Parkin is overwhelmed with mutant protein load in Gaucher disease cells. This leads to decreased ubiquitination of PARIS and ARTS, therefore increased accumulation and increased susceptibility to apoptosis under stress conditions.



The E3 ligase Itch regulates degradation of mutant glucocerebrosidase

Gali Maor, Israel

In diseases like Gaucher disease, the mutated gene produces a mutant glucocerebrosidase enzyme protein that is unable to fold properly and therefore undergoes ER associated degradation (ERAD). This process causes ER stress and the unfolded protein response.

Type 2 Gaucher disease is the most severe form of Gaucher disease. Affected neonates may develop ichthyosis due to hyper proliferation of the skin.

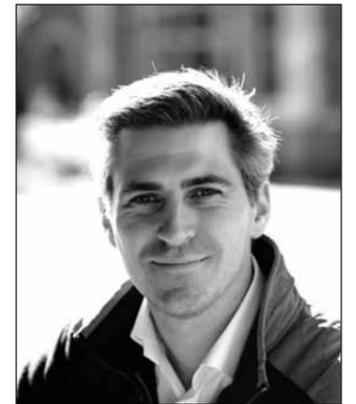
Dr Gali Maor from Israel showed interesting research findings on the Unfolded Protein Response (UPR). Mutant GCCase variants undergo ERAD the degree of which determines disease severity. Mutant GCCase is not a natural substrate for ubiquitination and proteasomal degradation, therefore it interacts with many different E3 ligases. Itch is an E3 ligase with a central role in the control of differentiation and proliferation of skin cells. Itch is involved in ubiquitination and degradation of both mutant GCCase and a transcription factor called Δ Np63. This research shows that elevation in GCCase levels in cells correlates with elevation of Δ Np63. The very attractive hypothesis is therefore that Itch is too busy dealing with the mutant GCCase in Gaucher cells and its natural substrate Δ Np63 accumulates. The cellular balance is therefore tipped towards hyper proliferation of the skin cells and the appearance of ichthyotic skin lesions in Gaucher disease type 2.



Psychosines implicated in the pathogenesis of Gaucher disease alter actin dynamics and perturb intracellular lysosomal trafficking

Jonathan Roos, UK

Psychosines have been shown to accumulate in Gaucher disease and may be responsible for its unusual phenotype. Dividing cells in lysolipid medium result in polyploidy but the mechanism is unknown. Dr Jonathan Roos from Cambridge, presented exciting data on the effect of β -glucosylsphingosine (or psychosine), on the cytoskeleton and cellular membrane trafficking. Diverse cells are affected by psychosine at variable concentrations. Treatment with psychosine reduces filopodia formation and results in small and large vesicle accumulation in the cytoplasm that mimic the electron microscope appearance of Gaucher cells. Fascinating electron microscope images were shown during this talk, proving that psychosine at pathophysiological levels can affect actin polymerisation. This pattern formation is unique to psychosine as opposed to a different type of actin toxin, jasplakinolide, that despite also inhibiting cytokinesis, does not produce the typical vesicles seen in Gaucher disease. These data show how basic research at the cellular and molecular level is crucial to the understanding of the pathogenesis of disease and instrumental to the development of targeted cell therapies with a clinical application.



Competition law and Gaucher and other orphan drug pricing

Hanna Hyry, Jonathan Roos and Timothy Cox, UK

Access to orphan products remains an acute problem in the EU and beyond. While the EU Orphan Regulation has been a success in bringing to the market effective treatments, the Regulation's 10-year marketing monopoly enables manufacturers to charge what some consider "exorbitant" prices for orphan products. This affects patients and their national health systems who struggle to finance treatments which may soon consume 6-8% of EU healthcare budgets. The current pricing model thus hinders access to treatment and contravenes the aim of the Regulation: namely to create parity of care between common and rare diseases. We have examined (BMJ.2010;341:c6471) whether EU competition law may be the solution to high pricing. Article 102 of the Treaty on the Functioning of the EU protects consumers from abuse of a dominant position by a company. Abuse includes unfair pricing and other unfair trading conditions. While the finding of abuse is a complex question of fact, we show that there is a credible general argument for violation of EU law by the current pricing practices. Competition law may however also inspire a less contentious resolution: the prospect of regulatory action could motivate a constructive dialogue on acceptable pricing levels. Such dialogue may better preserve incentives for the development of these life-saving treatments.



Invited Lecture: Investigation of a novel approach to treat patients with Gaucher disease

Roscoe Brady, USA

Nowadays Enzyme Replacement Therapy, substrate reduction, gene therapy and protein stabilization by chaperons are already the focus of research and therapy. Professor Brady and his working group are about to investigate novel strategies for therapy.

For a long time it was assumed that the alterations of the amino acid sequence which builds the enzyme glucocerebrosidase such as common mutations like L444P/L444P and N370S/N370S caused primarily reduction of the catalytic activity. Now they could find that the decrease of the enzyme activity is due at least in part to the reduction of its amount in cells caused by premature breakdown and transport defects. The point mutations result in the incorrect order of amino acids and by that a misfolding of glucocerebrosidase. This resulting abnormal 3D structure can't be tolerated by the cells and enzyme complexes called proteasomes eliminate mis-folded proteins in order to protect cells.

The quantity of enzyme was found to be reduced in cultured skin cells according to the different mutations. This reduced quantity was almost directly associated with the remaining activity of the enzyme in types of Gaucher patients. An explanation for this could be that the quality control of the cell compartment endoplasmic reticulum(ER) refuses to allow the mutant enzyme its normal pathway to lysosome where it breaks down glucocerebroside and instead leads it out of the ER to the proteasome to be destroyed. But even with an abnormal structure the enzyme there is still catalytic activity. So they tried to reduce the degradation of the enzyme by using histone deacetylase inhibitors and could find some beneficial effect such as a larger quantity of glucocerebrosidase in treated cells with Gaucher-associated mutations resulting in an increase of enzyme activity up to 50% in the N370S mutation. The use of histone deacetylase inhibitors appears to be a promising treatment strategy as they are able to cross the blood brain barrier and are an oral therapy. An immediate aim is a safety and dose response trial with the histone deacetylase inhibitors.



Activation of the unfolded protein response in Gaucher disease

Mia Horowitz, Israel

Mutant GCase variants undergo ERAD, which determines disease severity. Mutant enzyme molecules are recognised as misfolded proteins in the Endoplasmic Reticulum (ER), are then translocated to the cytoplasm and undergo there polyubiquitination and proteosomal degradation. Mutant molecules in the ER lead to ER stress and the Unfolded Protein Response (UPR). This process engages several cell pathways, which lead to up regulation in the expression of genes that are involved in apoptosis. The UPR machinery and its regulation may be crucial in the pathogenesis of Gaucher disease.

This study showed that UPR exists in Gaucher disease derived skin fibroblasts, as well as in cell that derived from carriers of GD mutations, by documenting up regulation of certain transcription factors and chaperones. It also showed direct effect of UPR on up regulation of the glucocerebrosidase gene, i.e. the production of more copies in response to the malfunctioning gene product, i.e. the mutant GCase enzyme.



Exploring bicyclic derivatives of L-idonojirimycin as pharmacological chaperones for the treatment of Gaucher disease

Pilar Alfonso, Spain

Dr Pilar Alfonso from Spain, showed us how exciting basic research can be translated into clinical treatment.

GCase mutants retain some enzymatic activity in vitro but suffer impaired cellular trafficking as a consequence of them being misfolded. Current therapeutic strategies include development of ligands of the enzyme capable of promoting conformational changes in its 3-dimensional structure, that are required for its efficient folding, thus promoting its trafficking.

Competitive inhibitors of GCase at subinhibitory concentrations can increase steady state lysosomal active GC acting as enzyme stabilisers otherwise known as pharmacological chaperones. Metabolic activity would be restored as competitive inhibition by the natural high concentration lysosomal substrate once the misfolded enzyme finds its way into its site of action, the lysosome.

Currently studied pharmacological chaperones are iminosugars that inhibit several cell glucosidases, not only glucocerebrosidase. Moreover, the GCase mutant needs to have an active site mutation for these compounds to act as effective chaperones. Some GC mutations outside the active site domain are associated with neurological involvement.

L-idonojirimycin derivatives synthesised from D-glucose after in-silico structural analysis and identification of the most favourable molecular features to interact with the active site of glucocerebrosidase. Chaperone potential was tested in vitro using a cell model of Gaucher disease containing the most frequently encountered mutations N370S or L444P. Increase in GC activity at various chaperone concentrations was shown, making these compounds very attractive as a potential therapeutic strategy in patients with neurological GD.



The pharmacological chaperone AT3375 alone and in combination with recombinant human acid β -Glucosidase for Gaucher disease

Elfrida Benjamin, USA

This study investigated the effects of a second generation pharmacological chaperone (PC), namely AT3375, on endogenous and exogenous GCase in vitro and in vivo.

AT3375 increased WT, N370S, and L444P GCase activity in patient-derived cells with 2- to 5-fold greater potency compared to AT2101. In wild type and mutant (L444P) mice, oral administration of this compound showed higher brain levels with more rapid clearance of AT3375 compared to the first generation PC, AT2101. AT3375 also increased brain GCase levels with 10-fold greater potency compared to AT2101. In L444P GCase mice, 4-week administration of AT3375 showed 2- to 3-fold greater increases in brain L444P GCase levels at lower doses compared to AT2101.

AT3375 stabilized exogenous recombinant human GCase (rhGCase) in vitro, minimizing its thermal denaturation and loss of activity at neutral pH and 37 °C. Co-administration of AT3375 with ERT in rats increased the circulating half life of rhGCase led to improved uptake in disease-relevant tissues.

These data implicate that AT3375 may have potential as a monotherapy for Gaucher disease with CNS involvement and may also improve the properties of rhGCase upon co-administration.



Long-term clinical outcomes in type 1 Gaucher disease following 10 years of Imiglucerase treatment

Stephan vom Dahl, Germany

Prof. Stephan vom Dahl reported the clinical outcome of 557 non-splenectomized and 200 splenectomized patients out of the ICGG Gaucher Registry which have been treated with imiglucerase/algucerase for at least 10 years. All patients are Gaucher disease Type I and the majority had at least one N370S allele. At baseline splenectomized patients had a higher percentage of bone pain and bone crises, a lower percentage of anaemia and thrombocytopenia and similar one in hepatomegaly.

After 2 years of treatment there was already a reduction of bone crises in nearly all patients and a reduction of bone pain in half of them. By the end of the 10 years all patients showed a significant improvement in all investigated clinical criteria. No severe types of hepatomegaly occurred anymore and only one patient with severe splenomegaly remained. So they conclude that enzyme replacement therapy with Imiglucerase is highly efficient and suited for individualized therapy



Plant-cell-expressed recombinant glucocerebrosidase – Taliglucerase-alfa as therapy for Gaucher disease in patients previously treated with Imiglucerase

Gregory Pastores, USA

Taliglucerase-alfa is a plant-cell-expressed human rhGCase in disposable bioreactors. Expression is free of mammalian components. In May 2012 it was approved by the US FDA as ERT for Gaucher disease.

This study was designed to assess the safety and efficacy of taliglucerase-alfa in GD patients previously treated with Imiglucerase. 26 adults GD patients were recruited for a period of 9 months, their mean age being 48 years. They were divided into 3 groups according to ERT dose (>30IU/kg, >15 and <30IU/kg and <15IU/kg). Following switch over, haemoglobin and platelet counts, liver and spleen size and chitotriosidase measurements remained stable or improved. Adverse events were mild or moderate in severity.

The study concludes that Taliglucerase-alfa was well tolerated and had similar efficacy to imiglucerase in patients with Gaucher disease switched over from imiglucerase



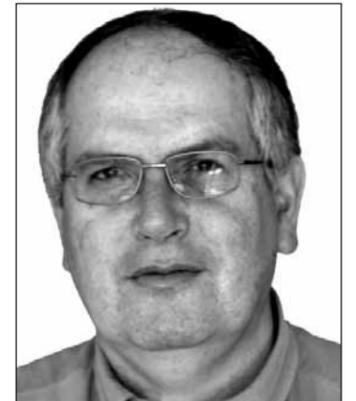
A multicentre, double-blind, randomized safety and efficacy study of two dose levels of Taliglucerase-alfa in paediatric subjects with Gaucher disease

Ari Zimran, Israel

Taliglucerase alfa is a recombinant glucocerebrosidase that is efficiently produced in plant cells and already approved as enzyme replacement therapy (ERT) for adult patients in the United States*. To investigate the safety and efficacy of the drug in children 11 patients aged between 2 and 18 years with newly diagnosed Gaucher disease (GD) received treatment for 12 month with either 30 or 60 units per kilogram during this trial. The safety was evaluated by observations for adverse events, antibody formation against the recombinant protein, clinical laboratory and echocardiography. The primary efficacy of the drug was measured in median percent change in haemoglobin from baseline. Other markers of efficacy were liver and spleen volume, platelet count and chitotriosidase. Exploratory endpoints included change of growth and development, bone disease and change in quality of life.

Within 12-months a significant increase of haemoglobin levels was measured in treated patients along with a reduction of liver and spleen size and increase of platelet count using the 60 units/kg/infusion. Improvement was also observed in parameters using the 30 units/kg/infusion dose but mostly on a lower level than the higher dose treated patients. The majority of adverse events were mild or moderate and all of transient nature. One treatment related serious adverse event was reported with symptoms of gastroenteritis. Changes in growth and development, bone disease and quality of life will be discussed in the future.

*since September 2012 also available in Israel.



The French Gaucher disease registry: Clinical characteristics, complications and treatment of 562 patients

Nadia Belmatoug, France

Gaucher disease clinical characteristics, complications and treatment drawn by analysing the French disease registry data, were presented in this very interesting talk by Dr Nadia Belmatoug.

The data were collected from GD patients who had at least one consultation between 1980 and 2010. 378 had identified follow-up.

562 GD patients were enrolled in the database. 49.5% were females, 85% had type 1 GD, 4.1% had type 2, 6.9% had the prenatal-lethal type and 3.9% had type 3.

Median age at first symptoms was 15 years and at diagnosis was 22 years for all GD types.

The first symptoms were splenomegaly and/or thrombocytopenia. Most patients were diagnosed by a bone marrow biopsy/aspiration. Enzyme deficiency was the investigation performed to confirm the diagnosis in all patients. The incidence was found to be 1/50,000. Major complications were bone events, splenectomy and Parkinson disease. 5% of the patients died. 12% had a monoclonal gammopathy. Among 283 patients 36 were untreated and 247 were treated. The study confirmed that bone events occurred with and without treatment and happened in 20% of the patients after 10 years. One third of the patient cohort were followed-up in the ile de France.

Interestingly, during the cerezyme supply shortage, half of the patients needed treatment.



Developing lentiviral vectors for gene therapy of type 1 Gaucher disease

Katherine Aitchison, PhD student, UK

Katherine Aitchison shared with us her fascinating research so far on gene therapy for Gaucher disease. Gene therapy in GD sounds like a very attractive option. ERT, the currently established therapy is not effective in treating bone disease and must be administered fortnightly.

Gene therapy and autologous transplantation of haemopoietic stem cells is an appealing treatment option.

Three lentiviral vectors carrying the GBA gene have been designed. Two contain versions of the GBA gene which are fused with the transduction domain of the HIV-1 TAT protein so that GBA is taken up independently of the mannose-receptor pathway.

Preliminary data show that all vectors express GBA enzyme by showing function of the enzyme within cells and presence of protein by western blot. Human embryonic kidney cells are transduced and active protein is secreted. The secreted enzyme can correct untransduced patient cells in a co-culture system (up to 4-fold increase in GBA activity in patient cell line)

Her future research plan is to test these lentiviral GBA vectors in material from GBA deficient mice and patient cells. She plans to study the differentiation of corrected haemopoietic cells to osteoclasts in an attempt to tackle the skeletal complications of GD.

In conclusion, so far, the UCL group have manufactured successful lentiviral vectors that have been shown to produce functional enzyme protein. The secretion and uptake of the enzyme protein has also been shown.

The results on osteoclast gene correction in the mouse model are eagerly awaited.

RARE DISEASE DAY
RARE DISORDERS WITHOUT BORDERS
February 28, 2013
www.rarediseaseday.org

New European Working Group on Gaucher Disease (EWGGD) Board

At the 10th EWGGD in Paris a new Board was elected for the period 2012-2014:

Prof. Dr. med. Stephan vom Dahl
*St. Franziskus-Hospital Köln Akadem.
Lehrkrankenhaus der Universität Köln
Schönsteinstrasse 63
50825 Köln, Germany
Tel: +49 221 5591 1101
Fax: +49 221 5591 1103
Email: innere@st-franziskus-koeln.de*

Dr. Helen Michelakakis
*Institute of Child Health, Ag. Sophia
Children's Hospital
Department of Enzymology and
Cellular Function
11527 Athens, Greece
Tel: +30 213 2037320
Fax: +30 210 7700111
Email: inchildh@otenet.gr*

Prof. Dr. Carla Hollak
*Academic Medical Center,
University of Amsterdam
Department of Internal Medicine
Div. of Endocrinology and Metabolism, F5-170
PO box 22700
1100 DE Amsterdam
The Netherlands
Tel: +31 20 5666071
Fax: +31 20 6917682
Email: c.e.hollak@amc.uva.nl*

Prof. Dr. Timothy Cox
*Addenbrooke's Hospital
Department of Medicine
University of Cambridge
Box 157, Level 5
Cambridge CB2 0QQ, UK
Tel: +44 1223 336864
Fax: +44 1223 336846
Email: tmc12@medschl.cam.ac.uk*

Jeremy Manuel
*Manuel Swaden Solicitors
340 West End Lane
London NW6 1LN
United Kingdom
Tel: +44 20 7431 4999
Fax: +44 20 7794 9900
Email: JeremyM@manuelswaden.co.uk*

Dr. Hanna Rosenbaum
*Rambam Health Care Campus
Hematology and Bone Marrow
Transplantation Department
Haifa
Israel
Tel: +972 4 8542 541
Fax: +972 4 8541514
Email: h_rosenbaum@rambam.health.gov.il*

Dr. Mia Horowitz
*Tel Aviv University
Dept. Cell Research and Immunology
Ramat Aviv 69978
Israel
Tel: +972 3 6409 285
Fax: +972 3 6422 046
Email: horwitzm@post.tau.ac.il*



Preliminary Announcement

The 11th European Working Group on
Gaucher Disease (EWGGD)
will be held in Haifi, Israel
25-28 June 2014.

For further information please contact:
Dr Hanna Rosenbaum at
h_rosenbaum@rambam.health.gov.il



About the European Gaucher Alliance (EGA)



The EGA is a pan-European umbrella group representing the interest of Gaucher patients and those of not-for-profit Gaucher patient groups throughout Europe and elsewhere in the world.

The aims and objectives of the EGA are:

- To collect information on the latest developments in the understanding, management and treatment of Gaucher Disease and to disseminate such information to all parties who have an interest in Gaucher Disease and other similar disorders.
- To provide information, support, guidance and encouragement to groups of individuals representing Gaucher patients throughout Europe and elsewhere in the world.
- To represent the interests of Gaucher patients to European and international organisations and bodies and to ensure that the voice of the Gaucher patient is heard at all times.
- To encourage and promote scientific and medical research into Gaucher Disease and improved therapeutic approaches, and to seek to ensure all such research recognises the centrality of the Gaucher patient.
- To work with the medical and scientific community to define priorities in the understanding of Gaucher Disease, its management and treatment.
- To work with, facilitate, support and encourage the activities of the European Working Group on Gaucher Disease (EWGGD) and other organisations or working groups with similar objectives.
- To be a forum to address ethical issues arising from the study of Gaucher Disease, its management and treatment.
- To ensure that appropriate treatment is available to all patients with Gaucher Disease who require treatment regardless of race, creed, colour ethnic origin or national or religious background.

Members of the Management Council

A new board of directors was elected at the EGA meeting on 27th June 2012 in Paris, France.

The members elected were:

- | | |
|--------------------------------------|--------------------------------|
| 1. Yossi Cohen (Israel) | 6. Johanna Parkkinen (Finland) |
| 2. Tanya Collin-Histed (UK) | 7. Radoslava Tomova (Bulgaria) |
| 3. Anne-Grethe Lauridsen (Denmark) | 8. Sandra Zarina (Latvia) |
| 4. Jeremy Manuel OBE (UK) - Chairman | 9. Irena Žnidar (Slovenia) |
| 5. Pascal Niemeyer (Germany) | |

Membership

Although the EGA is a European organisation, it has always accepted responsibility to help and support Gaucher patients and patient groups from all parts of the world and aims to continue in this role.

Beside the original founding associations of the EGA (the UK, Italy, Netherlands, Israel, France and Sweden), full membership is available to all European 'not for profit' Gaucher organisations or umbrella groups representing the interest of patients suffering from rare diseases, which are under the control of patients.

Patient groups from non-European countries can apply to be associate members of the EGA, but will not have voting rights.

EGA member countries:

Austria; Belgium; Bosnia & Herzegovina; Bulgaria; Czech Republic; Denmark; Estonia; Finland; France; Germany; Greece; India; Ireland; Israel; Italy; Jordan; Latvia; Lithuania; Macedonia; Mexico; Netherlands; Norway; Poland; Romania; Russia; Serbia; Slovakia; Slovenia; South Africa; Spain; Sweden; Switzerland; Ukraine; UK; USA

For more information, or to join the EGA, please contact any of the Council Members known to you or email admin@eurogaucher.org.