11TH EWGGD HAIFA
The European Working Group on Gaucher Disease

ABSTRACT BOOK

TABLE OF CONTENTS

Dear Friends, Dear Colleagues,

It is a great pleasure and honor to welcome you to the 11th EWGGD meeting in Haifa, my hometown, and the capital of northern Israel.

On behalf of the organizing committees I would like to express our gratitude for the participation and contribution of delegates arriving from five continents of the world. Under the Haifa sky and overlooking the beautiful bay we expect a program with innovations in basic, clinical and translational science regarding Gaucher disease. Having attendees who are leading experts and researchers in the field, we should all be very proud and excited about where we are headed in the present gathering.

Our faculty and invited speakers will enrich us with new insights into population genetics, pathophysiology of neuropathic disease and new aspects of therapy.

Dear members of the European Gaucher Alliance (EGA): I would like to welcome each and every one of you. We all acknowledge your landmark event, as we will be celebrating the EGA's 20th Anniversary.

I also would like to welcome and extend a special thank to our dear friends from the pharmaceutical companies for their kind contribution and generous support. Before I close, I wish you an enjoyable event and stay in Haifa with fruitful discussions and accomplishments of future collaborations. I also would like to extend a special thank to my staff, EWGGD board members, scientific committee and the local secretariat from Palex tours.

My personal respect and thanks goes out to all of you.

Hanna Rosenbaum MD

SCIENTIFIC COMMITTEE

Stephan vom Dahl, Prof
Dept. of Gastroenterology, Hepatology and Infectious Diseases
University Hospital Duesseldorf
Moorenstrasse 5, 40225 Duesseldorf, Germany; stephan.vomdahl@med.uni-duesseldorf.de

Hanna Rosenbaum, Clinical Assistant Prof
Director, Hematology, Day Care Unit
Director, Center for Gaucher disease for the north of Israel
Rambam Health Care Campus, Haifa, Israel; E-mail: h_rosenbaum@rambam.health.gov.il

Mia Horowitz, Prof
Department of Cell Research and Immunology
Tel Aviv University, Ramat Aviv, 69978 Israel; E-mail: horwitzm@post.tau.ac.il

Helen Michelakakis, PhD
Head of Department of Enzymology and Cellular Function
Institute of Child Health, Athens, Greece; E-mail: hel.mikaki@gmail.com

EXECUTIVE COMMITTEE

- Chairman: **Stephan vom Dahl,** Prof, University Hospital Dusseldorf, Germany
- Vice-chairman: **Helen Michelakakis,** PhD, Institute of Child Health, Athens, Greece

Hans Aerts, Prof, Academic Medical Center, University of Amsterdam, the Netherlands

Timothy Cox, Prof, Addenbrooke's Hospital, Cambridge, UK

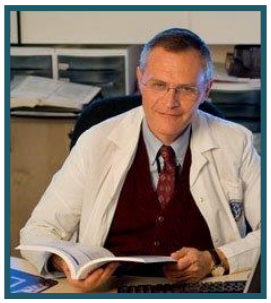
Mia Horowitz, Prof, Tel Aviv University, Israel

Jeremy Manuel, OBE, European Gaucher Alliance (EGA), UK

Hanna Rosenbaum, MD, Rambam Health Care Campus, Haifa, Israel (EWGGD 2014 host)

Marieke Biegstraaten, MD, PhD, Academic Medical Center, University of Amsterdam, The Netherlands

INVITED SPEAKERS



Karl Skorecki was born and raised in Toronto, the only child of holocaust survivors. He studied medicine at the University of Toronto, where he graduated in 1977 with a Gold Medal for highest overall standing in the Faculty, including awards for first standing in many other courses. Karl pursued post-graduate clinical and research training in Boston, at Brigham and Women's hospital and at the Massachusetts General Hospital. He served as Chief Resident in Medicine at the Brigham in 1981-82 academic year, where he was also awarded the George G. Thorn Teaching Prize. Dr. Barry Brenner served as Karl's research mentor at the Brigham, in the area of biology of the kidney in health and disease. In 1984 Karl was appointed to the Faculty of the University of Toronto in the Division of Nephrology, where he established a productive original research program in the areas of kidney disease, molecular biology, and human genetics. He was subsequently appointed as Professor and Director of the Division of Nephrology in the Departments of Medicine, Pediatrics, and Clinical Biochemistry at the University of Toronto, and Research Scientist and Director of the Nephrology Division at the Hospital for Sick Children in Toronto. After spending a sabbatical at the Weizmann Institute in the first half of 1991 (overlapping the first gulf war), Karl and his family decided to fulfill their lifelong ambition of moving to Israel.
In 1995, Skorecki joined the staff of Rambam Health Care Campus (Rambam) and the Technion-Israel Institute of Technology's (the Technion) Ruth and Bruce Rappaport Faculty of Medicine in Haifa. Between the years 1995-2005, he served as Director of Rambam's Nephrology Department.
Karl is currently Director of Medical and Research Development at Rambam and Director of the Rappaport Research Institute of the Technion. He conducts research in human molecular genetics and stem cell biology.

Karl's research program has spanned numerous areas of activity, most recently focusing on population health and population genetics, as well as stem cell biology, among other areas. This research program has attracted numerous graduate students and research fellows, who have obtained postgraduate degrees under his supervision. The research program has also attracted funding from major international competitive research granting agencies, and has led to more than 200 publications, numerous presentations at international scientific meetings, and more than 90 invited lectureships or visiting professorships at major academic centers and conferences throughout the world. He serves as lead editor for The Kidney, and has contributed chapters for the past several editions of Harrison's and Cecil textbooks of medicine – in the areas of kidney disease, fluid and electrolyte disorders, and cell and gene therapy. He has been awarded prizes for his research findings and biomedical innovations.

Karl met his wife Linda Welkovics at a Jewish summer camp in Ontario in 1971, and they were married in 1975. Linda and Karl have five children, and fourteen grandchildren, all living in Haifa, Israel.

Ellen Sidransky, Chief of the Section of Molecular Neurogenetics, is a pediatrician and clinical geneticist in the Medical Genetics Branch of the National Human Genome Research Institute at the National Institutes of Health in Bethesda, Maryland. Dr. Sidransky graduated Magna Cum Laude from Brandeis University with a B.A. in biology, and received her M.D. from Tulane University. She then trained in pediatrics at Children's Memorial Hospital/Northwestern University, and completed fellowship training in clinical genetics at the NIH Genetics Training Program. Dr. Sidransky has been a tenured investigator at NIH and a Section Chief since 2000. Her research includes both clinical and basic research aspects of Gaucher disease and Parkinson disease, and her group first identified glucocerebrosidase as a risk factor for parkinsonism. She has spearheaded two large international collaborative studies regarding the genetics of Parkinson disease and dementia with Lewy bodies. Her current work also focuses on understanding the complexity encountered in "simple" Mendelian disorders, the association between Gaucher disease and parkinsonism and the development of small molecule chaperones as therapy for Gaucher disease and potentially parkinsonism. Dr. Sidransky directs two NIH clinical protocols, one evaluating patients with lysososmal storage disorders and the second prospectively studying patients and relatives with parkinsonism who carry mutations in GBA.

Tony Futerman received his B.Sc. degree in Biochemistry at the University of Bath, England, in 1981, and then moved to the Department of Neurobiology in the Weizmann Institute of Science, Israel, for his doctoral studies. From 1987-1990, he was a postdoctoral fellow in the laboratory of Dr. R. Pagano in Baltimore, USA, where he analyzed the sites of synthesis of sphingolipids. He is currently a Full Professor in the Department of Biochemistry in the Weizmann Institute of Science where he runs a laboratory of ~20 scientists, postdoctoral fellows and students that work on sphingolipid synthesis and on lysosomal storage diseases (mainly Gaucher disease), and is head of the Nella and Leon Benoziyo Center for Neurological Diseases. Tony Futerman was a member of the board of the Journal of Biological Chemistry from 2002-2012, and was the chair of the 2006 Gordon Conference on Glycolipid and Sphingolipid Biology and chair of the 2011 Gordon Conference on Lysosomal Diseases.

Sophia Ish-Shalom, M.D. has been the Head of the Metabolic Bone Diseases Unit at Rambam Medical Center in Haifa, Israel, since 1995. Prof. Ish-Shalom is an Associate Professor of Endocrinology at the Bruce Rappaport Faculty of Medicine at the Technion-Israel Institute of Technology. She has over 30 years of clinical and research experience in Israel and Canada and has published over 40 articles on osteoporosis research in leading scientific journals. She serves as a Member of Clinical advisory board of TransPharma Medical Ltd. She is a member of the committee of the Israeli Endocrine Society and the Israeli Foundation for Osteoporosis and Bone Diseases as well as Head of the Israeli Association of Medical Women. She also heads the Committee on Diagnosis and Treatment of Osteoporosis at the Israeli Ministry of Health, and is a member of the American Society for Bone and Mineral Research and the American Endocrine Society. Prof. Ish-Shalom holds an M.D. from the Technion-Israel Institute of Technology and is Board certified in both Internal Medicine and Endocrinology in Israel.

Scientific program here

SOCIAL EVENTS

Wednesday, June 25, 2014

15:00 -	**Check-in time to hotels**	
15:00 - 19:30	**Registration desk & distribution of materials**	*(Dan Carmel Lobby)*
19:00 -	**Welcome reception**	*(Dan Carmel Garden)*

Thursday, June 26, 2014

07:00 – 15:00	**Registration desk & distribution of materials**	*(Dan Carmel Lobby)*
08:30 – 15:40	**Scientific Program**	*(Dan Carmel, King David hall)*
16:00	**Meeting point; according to prearranged grouping**	*(Dan Carmel)*
16:00 – 18:30	**Guided tour of Haifa** *Panoramic view, the German Colony, Stella Maris* *To be followed by drive to Caesarea*	
19:30 –	**Dinner & Dance**	*(Dan Caesarea hotel)*

Friday, June 27, 2014

08:00 – 17:00	**Registration & hospitality desk** Time for dealing with financial matters (travel grants, payments, inquiries, reimbursements)	*(Dan Carmel Lobby)*
08:30 – 17:00	**Scientific Program**	*(Dan Carmel, King David hall)*
20:00 -	**Gala Dinner** Celebrating the 20th Anniversary of the EGA	*(Dan Carmel, King David hall)*

Saturday, June 28, 2014

08:00 – 15:00	**Registration & hospitality desk**	*(Dan Carmel Lobby)*
08:30 – 14:00	**Scientific Program**	*(Dan Carmel, King David hall)*
14:00	**Meeting Adjourned**	

INVITED SPEAKERS PRESENTATIONS

1 **Genetic History of the Jewish People**
Karl Skorecki

2 **Induced pluripotent stem cell models of Gaucher disease provide new insights into pathogenesis and therapy**
Ellen Sidransky

3 **RIPK3 as a potential therapeutic target for Gaucher disease**
Tony Futerman

Thursday, June 26, 2014, 09:15-10:00

Genetic History of the Jewish People

Karl Skorecki

"Genomic Science" refers to a scholarly discipline gleaned from the study of the biochemical polymer deoxyribonucleic acid (DNA) in all its manifestations and application. The discovery of DNA as the universal molecular basis for heredity in the 1940s, and the subsequent resolution of its structure in 1953, has fuelled six exciting decades of advancement at an ever accelerating pace in the biological sciences, and in medical genetics. Population history is an additional scholarly field that has more recently benefited from study of DNA. The enabling power of DNA studies encompasses studies of the origins of humans (genetic anthropology), demographic history (populations genetics), reconstruction of family trees (genetic genealogy), and questions of individual identity (forensic genetics). The respective timeframes range from hundreds of thousands of years, to contemporary times. This presentation will focus on what we have learned from Genomic Science with respect to the history of the Jewish people, capturing a window ranging from a few centuries to a few millennia. It should be emphasized at the outset, that genomic science should be reviewed as an adjunctive tool, alongside the more longstanding conventional tools used by scholars of population history and demographics. These classic tools include archeology, study of archival records, linguistics, and the comparative study of narratives. It is noteworthy that utilization of Genomic Science achieves its maximum value when taken together and in conjunction with the rich panoply of these and other approaches and methods in the study of human history.

Thursday, June 26, 2014, 13:45-14:30

Induced pluripotent stem cell models of Gaucher disease provide new insights into disease pathogenesis and therapy

Elma. Aflaki,[1] Barbara. K. Stubblefield,[1] Grisel Lopez,[1] Nima Moaven, [1] Wendy Westbroek,[1] Juan Marugan,[2] Samarjit Patnaik,[2] Nahid Tayebi,[1] and Ellen Sidransky[1]

[1]Section of Molecular Neurogenetics, Medical Genetics Branch, and [2]National Center for Advancing Translational Sciences, National Institutes of Health, Bethesda MD, USA

Studies into the pathogenesis and treatment of Gaucher disease have long been impeded by the lack of appropriate cell-based models exhibiting cellular changes analogous to those seen in patient macrophages and neurons. We established a Gaucher disease macrophage model exhibiting glycolipid storage by generating induced-pluripotent stem cells from type 1 and type 2 Gaucher fibroblasts. Gaucher, but not control iPSC-derived macrophages had reduced glucocerebrosidase activity and exhibited significant glycolipid storage, further enhanced by adding tagged glycolipids and lipid-rich erythrocyte ghosts prepared from patient samples. Using this model we show that Gaucher macrophages manifest efficient phagocytosis, but have defects in chemotaxis. Moreover, reduced intracellular reactive oxygen species production and impaired phagosome maturation in these Gaucher cells caused defective digestion of phagocytic material and resulted in the suppression of autophagy, providing new insights into defects related to this disorder.

The Gaucher macrophage model was then used to validate the efficacy of a novel non-inhibitory chaperone molecule, identified by high throughput screening of large compound libraries using mutant N370S glucocerebrosidase from patient tissue extracts. Our lead compound enhanced glucocerebrosidase activity and the translocation of glucocerebrosidase to lysosomes, reduced lipid storage and normalized chemotaxis in Gaucher macrophages. Thus, both our lead compound and new macrophage models can be used to accelerate research into new therapeutics for Gaucher disease.

Since mutant glucocerebrosidase is implicated in the pathogenesis of Parkinson disease and related disorders, further development of such enzyme-enhancing therapies could have implications for the treatment of different forms of parkinsonism. We generated dopaminergic neurons from patient iPSCs, including lines from patients with Gaucher disease and parkinsonism. The Gaucher neurons produced the appropriate catecholamine metabolites, showed dopamine reuptake, exhibited glucocerebrosidase deficiency and had elevated levels of alpha-synuclein. Upon treatment with the lead chaperone, glucocerebrosidase activity was restored and alpha-synuclein levels were reduced, extending the implications of our findings beyond Gaucher disease.

Friday, June 27, 2014, 08:30-09:15

RIPK3 as a potential therapeutic target for Gaucher disease

Tony Futerman

Department of Biological Chemistry, Weizmann Institute of Science, Rehovot 76100, Israel
email: Tony.Futerman@weizmann.ac.il
http://www.weizmann.ac.il/Biological_Chemistry/scientist/futerman/

Glucosylceramide (GlcCer) and glucosylsphingosine accumulation in the brain leads to massive neuronal loss in neuronopathic GD (nGD) patients and in nGD mouse models. However, the mode of neuronal death is not known. We recently demonstrated elevation of pro-inflammatory cytokines, including interleukin-1 beta (IL-1β) and tumor necrosis factor-a (TNFa in a mouse model of Gaucher disease, the *Gba*$^{flox/flox}$;Nestin-Cre mouse, a mouse that recapitulates many of the features of the neuronopathic human disease, although *Gba1* deficiency is restricted to neural and macroglial lineages in this mouse. Our data suggested that neuroinflammation induces cytotoxic effects in nGD. Inflammation is usually associated with necrotic rather than apoptotic cell death; cell death via necrosis leads to microglial activation and pro-inflammatory signaling cascades. I will now discuss our recent data that shows that modulating the receptor-interacting protein kinase 3 (Ripk3) pathway markedly improves neurological and visceral disease in a mouse model of Gaucher disease. Importantly, *Ripk3* deficiency dramatically improved the clinical course of Gaucher disease mice with increased survival, motor coordination and salutary effects on cerebral as well as hepatic injury. I will also discuss additional data demonstrating the involvement of a number of other pathways in Gaucher disease pathology and suggest that these too might act as therapeutic targets.

Selected recent references

1. Vitner, E., Platt, F.M. and Futerman, A.H. (2010) Common and uncommon pathogenic cascades in lysosomal storage diseases. *J. Biol. Chem*., **285**, 20423-20427.
2. Farfel-Becker, T., Vitner, E.B., Pressey, S.N.R., Eilam, R., Cooper, J.D. and Futerman. A.H. (2011) Spatial and temporal correlation between neuron loss and neuroinflammation in a mouse model of neuronopathic Gaucher disease. *Hum. Mol. Genet.* **20**,1375-86
3. Farfel-Becker, T., Vitner, E.B. and Futerman. A.H. (2011) Animal models for Gaucher disease research. *Disease Models and Mechanisms*, **4**, 746-752.
4. Vitner, E.B., Biton, I., Farfel-Becker, T. and Futerman, A.H. (2012) Contribution of brain inflammation to neuronal cell death in neuronopathic forms of Gaucher disease. *Brain*, **135**, 1724-1735
5. Farfel-Becker, T., Vitner, E.B., Kelly, S.L., Bame, J.R., Duan,J., Shinder, V., Merrill, A.H. Jr., Dobrenis, K. and Futerman, A.H. (2013) Neuronal accumulation of glucosylceramide in a mouse model of neuronopathic Gaucher disease leads to neurodegeneration. *Human Molecular Genetics*, **23**, 843-854.
6. Vitner, E.B., Salomon, R., Farfel-Becker, T., Meshcheriakova, A., Ali, M., Klein, A.D., Platt, F.M., Cox, T.M. and Futerman, A.H. (2014) RIP3 as a potential therapeutic target for Gaucher disease. *Nature Medicine*, 20, 204-209.

ORAL PRESENTATIONS

O-01	**Thirty years' experience of allogeneic bone marrow transplantation for Gaucher disease type 3 in Sweden** *Machaczka, M., Kämpe Björkvall, C., Markuszewska-Kuczyńska, A., Klimkowska, M., Myhr-Eriksson, K., Hägglund, H., Ringdén, O. - SWEDEN*
O-02	**Impact of long term ERT in child, the Spanish experience** *Andrade, M., Alfonso, P., Irún, P.,Dalmau, J., Barbera, J.L., Cano, H., Fernandez-Galán, M.A., Franco, R., Gracia, I., Ibañez, A., Lendines, F., Martin-Hernández, E., Pérez del Soto, A., Pérez-Calvo, J.I., Sancho-Val, I., Sanjurjo, P., Pocovi, M., Giraldo, P. - SPAIN*
O-03	**Spinal deformities in Norrbottnian type 3 Gaucher disease: prevalence, possible etiology, and management options** *Lebel, E., Kämpe Björkvall, C., Nilsson, M., Klimkowska, M., Myhr-Eriksson, K., Elstein, D., Svenningsson, P., Machaczka, M. – ISRAEL, SWEDEN*
O-04	**Chronic neuronopathic Gaucher disease: outcomes, morbidity in the Mainz cohort** *Mengel, E., Arndt, J., Brixius-Huth, M., Bremova, T., Naumann, S. and Reinke, J. - GERMANY*
O-05	**The impact of ERT on immunity in Gaucher disease** *Komlodi-Pazstor,E., Limgala, R., Martin, C., Hebert, A., Brown, M., Plassmeyer, M., Ryherd, M., Austin, L., Alpan, O., and Goker-Alpan, O. - USA*
O-06	**Monocyte dysfunctional migration in Gaucher's disease** *Bettman, N., Katz, T., Avivi, I., Chen Zion, Y., Rosenbaum, H. - ISRAEL*
O-07	**Aberrant differentiation and impaired lysosomal functions revealed by Gaucher-specific induced pluripotent stem cells (iPSC)** *Panicker, L.M., Sgambato, J.A., Awad, O., Miller, D. and Feldman, R.A. - USA*
O-08	**A role for GBA2 in neuropathology in Niemann-Pick type C** *Marques, A.R.A., Aten, J., Ottenhoff, R., van Roomen, C.P.A.A., Claessen, N., Mirzaian, M., Boot, R.G., Yildiz, Y., Overkleeft, H.S., Aerts, J.M.F.G. – the NETHERLANDS*
O-09	**System-wide involvement in Gaucher disease: role of GBA2 and downstream lipids** *Mistry, P.K., - USA*
O-10	**Glycolipid abnormalities in Gaucher disease: is there more to learn?** *Aerts, J.M.F.G. – the NETHERLANDS*
O-11	**Unusual presentations of Gaucher disease** *Rosenbaum, H. - ISRAEL*
O-12	**The prevalence of Gaucher in idiopathic splenomegaly is 1.50: follow-up of a nationwide screening study in 200 patients** *vom Dahl, S., Bange, M., Merkel, M., Voßbeck, J., Mengel, E., Herrmann, A., Donner, M., Santosa, D., Häussinger, D. - GERMANY*
O-13	**High prevalence of small fibre neuropathy in type 1 Gaucher disease** *Devigili, G., Ciana, G., Sechi, A., Deroma, L., Dardis, A., Zampieri, S., Deganuto, M., Cattarossi, S., Pianta, A., De Filippo, M., Lettieri, C., Rinaldo, S., Eleopra, R., Bembi, B. - ITALY*
O-14	**Whole-body MRI iron level measurement in Gaucher disease** *Regenboog, M., Akkerman, E.M., Stoker, J., Hollak, C.E.M. – the NETHERLANDS*
O-15	**Prevalence of autoantibodies in the course of Gaucher disease type 1** *Serratrice, C., Bensalah, N., Belmatoug, N., Masseau, A., Rose, C., Kaminsky, P., Lidove, O., Camou, F., Maillot, F., Leguy Seguin, V., Bertrand, N.M., Marie, I., Cabane, J., Alessandrini, M., Bardin, N., Boucraut, J., Berger, M. - FRANCE*
O-16	**An unsuspected dyserythropoiesis in Gaucher disease** *Reihani, N., Arlet, J.B., Billette de villemeur, T., Belmatoug, N., Colin, Y., Hermine, O., LeVan Kim, C. & Franco, M. - FRANCE*
O-17 (a&b)	**(a)The origins of glucsylsphingosine and (b)LC-MS/MS quantification of glucosylsphingosine in urine and plasma of type 1 Gaucher patients using an isotope standard** *(a) Ferraz, M.J., Appelman, M.D., Verhoek, M., Strijland, A., Scheij, S., Ouairy, C., Boot, R., Aerts, J.M. – (b)Mirzaian, M., Wisse, P., Ferraz, M.J., Gold, H., Donker-Koopman, W.E., Verhoek, M., Overkleeft, H.S., Boot, R.G., Kramer, G., Dekker, N., Aerts J.M.F.G. – the NETHERLAND*

O-18	**Taliglucerase alfa in adult patients with Gaucher disease who were previously treated with imiglucerase: 36-month safety and efficacy results** *Pastores, G.M., Shankar, S.P., Petakov, M., Giraldo, P., Rosenbaum, H., Amato, D.J., Szer, J., Chertkoff R., Brill-Almon, E., Zimran, A. – IRELAND, USA, SERBIA, SPAIN, ISRAEL, CANADA, AUSTRALIA*
O-19	**Platelet count and chitotriosidase activity in patients with type 1 Gaucher disease who were switched from imiglucerase to velaglucerase alfa** *Elstein, D., Zimran, A., Hughes, D.A., Giraldo, P., Charrow, J., Smith, L., Shankar, S.P., Kunes, Y., Wang, N., Dinh, Q., Crombez, E., Mehta, A. – ISRAEL, UNITED KINGDOM, SPAIN, USA*
O-20	**Seven-year follow-up in a phase I/II trial and open-label extension study for velaglucerase alfa in treatment-naïve adults with type 1 Gaucher disease** *Elstein, D., Wang, N., Ogg, C., Crombez, E., Cohn, G.M., Zimran, A. – ISRAEL, USA*
O-21	**The UPR-associated transcription factor CHOP upregulates expression of the GBA gene** *Maor, G., Braunstein, H. and Horowitz, M. - ISRAEL*
O-22	**Taliglucerase alfa 36-month clinical safety and efficacy in treatment-naïve patients** *Zimran, A., Durán, G., Mehta, A., Giraldo, P., Rosenbaum, H., Giona, F., Amato, D.J., Petakov, M., Terreros Muñoz, E., Solorio-Meza, S.E., Cooper, P.A., Chertkoff, R., Brill-Almon, E. – ISRAEL, CHILE, UNITED KINGDOM, SPAIN, ITALY, CANADA, SERBIA, MEXICO, SOUTH AFRICA*
O-23	**ENGAGE: A phase 3, randomized, double-blind, placebo-controlled, multi-center study to investigate the efficacy and safety of eliglustat in adults with Gaucher disease type 1: 18-month results** *Baris, H., Mistry, P.K., Lukina, E., Ben Turkia, H., Ghosn, M., Mehta, A., Petakov, M., Danda, S., Hadjiev, E., Angell, J., Ross, L., Peterschmitt, M.J. – ISRAEL, USA, RUSSIA, TUNISIA, LEBANON, UNITED KINGDOM, SERBIA, INDIA, BULGARIA*
O-24	**ENCORE: A randomized, controlled, open-label non-inferiority study comparing eliglustat to imiglucerase in Gaucher disease type 1 patients stabilized on enzyme replacement therapy: 24-month results** *Peterschmitt, M.J., Cox, T.M., Drelichman, G., Cravo, R., Balwani, M., Burrow, T.A., Martins, A.M., Lukina, E., Rosenbloom, B., Ross, L., Angell, J., Puga, A.C. – USA, UNITED KINGDOM, ARGENTINA, BRAZIL, USA, RUSSIA*
O-25	**Cost-effectiveness studies in Gaucher and Fabry disease** *Hollak, C., Biegstraaten, M., van Dussen, L., Rombach, S., Dijkgraaf, M. – the NETHERLANDS*
O-26	**Novel treatment for Gaucher disease - oral administration of plant cells expressing GCD: Phase 1 study results and Phase 2a program** *Zimran, A., Rosenbaum, H., Golembo, M., Velitski, S., Kivity, V., Chertkoff, R., Almon, E., Shaaltiel, Y. - ISRAEL*
O-27	**Identification of microRNAs that modulate glucocerebrosidase activity in Gaucher disease cells** *Siebert, M., Westbroek, W., Chen, Y-C., Moaven, N., Li, Y., Velayati, A., Saraiva-Pereira, M.L., Martin, S. and Sidransky, E. – USA, BRAZIL*
O-28	**Gaucher disease and parkinsonism: longitudinal clinical characterization and prognosis** *Lopez, G., Kim, J., Groden, C., Wiggs, E., Tayebi, N., Gonzalez, A., Sidransky, E. USA*
O-29	**Comparison of Parkinson risk in Ashkenazi Jewish patients with Gaucher disease and GBA heterozygotes** *Dinur, T., Quinn, T., Sakanaka, K., Levy, O., Waters, C., Fahn, S., Dorovski, T., Chung, W.K., Pauciulo, M., Nichols, W., Rana, H.Q., Balwani, M., Bier, L., Elstein, D., Zimran, A., Alcalay, R.N.*
O-30	**Disruption of monoamine metabolism in lysosomal storage disorders: a mechanistic link to Parkinson's disease?** *Heales, S., Burke, D., Neergheen, V. and Pope, S. - United Kingdom*

O-31	**The connection between ERAD, UPR, Gaucher disease and Parkinson's disease** *Horowitz, M., Braunstein, H., Enoch, M. and Maor, G. - ISRAEL*
O-32	**Visualization of active glucocerebrosidases in rodent brain with high spatial resolution by fluorescent activity based probes** *Herrera Moro Chao, D., Kallemeijn, W.W., Orre, M., Ottenhoff, R., Van Roomen, C., Foppen, E., Renner, M., Marques, A., Moeton, M., Siljee, J., Van Eijk, M., Boot, R., Kalsbeek, A. and Aerts, J.M.F.G. – the NETHERLANDS*
O-33	**The effect of protease inhibition on lysosomal glucocerebrosidase** *Oussoren, S.V., Scheij, S., Ferraz, M.J., Boot, R.G., Aerts, J.M.F.G. – the NETHERLANDS*
O-34	**Bone assessment in Spanish type 1 Gaucher disease patients: The ZAGAL project** *Andrade, M., Alfonso, P., Irun, P.,Garcia-Frade, J., Lorenzo, J.F., Luño, E., Martin,.E., Puerta, J., de la Serna, J., Villalon, L., Pocovi, M., Roca, M., Giraldo, P. - SPAIN*
O-35	**Changes in peripheral blood osteoclast cultures in relation to features of bone disease in adult GD1 patients** *Cunningham, N., Bauernfreund, Y., Reed, M., Mehta, A.B., Hughes, D.A. – UNITED KINGDOM*
O-36	**Proinflammatory and proosteoclastogenic potential of peripheral blood mononuclear cells from Gaucher patients: implication for bone pathology** *Mucci, J.M., Cuello, M.F., Kisinovsky, I., Larroude, M., Delpino, M.V.; Rozenfeld, P. - ARGENTINA*
O-37	**Can we quantify how effective is the treatment for Gaucher disease? Lessons from a COCHRANE review** *Shemesh, E., Deroma, L., Bembi, B., Deegan, P., Hollak, C., Weinreb, N.J., Cox, T.M. – ISRAEL, ITALY, UNITED KINGDOM, NETHERLANDS, USA*
O-38	**Limits on use of health economic assessments for rare diseases** *Hyry, H.I., Stern, A.D., Cox, T.M., Roos, J.C.P. – UNITED KINGDOM, USA*
O-39	**The legal imperative for treating rare disorders** *Hyry,H.I., Roos, J.C.P., Manuel, J., Cox, T.M. – UNITED KINGDOM*

O-01

THIRTY YEARS' EXPERIENCE OF ALLOGENEIC BONE MARROW TRANSPLANTATION FOR GAUCHER DISEASE TYPE 3 IN SWEDEN

Machaczka, M.[1,2,†], Kämpe Björkvall, C.[3], Markuszewska-Kuczyńska, A.[1], Klimkowska, M.[4], Myhr-Eriksson, K.[3], Hägglund, H.[1, 2], Ringdén, O.[5,6]

[1]Hematology Center Karolinska, Karolinska University Hospital Huddinge, Stockholm, Sweden; [2]Department of Medicine at Huddinge, Karolinska Institutet, Stockholm, Sweden; [3]Department of Medicine, Sunderby Regional Hospital of Norrbotten County, Luleå, Sweden; [4]Department of Clinical Pathology and Cytology, Karolinska University Hospital Huddinge, Stockholm, Sweden; [5]Division of Transplantation Surgery, Department of Clinical Science, Intervention and Technology, Karolinska Institutet, Karolinska University Hospital Huddinge, Stockholm, Sweden; [6]Center for Allogeneic Stem Cell Transplantation, Karolinska Institutet, Karolinska University Hospital Huddinge, Stockholm, Sweden, †Presenting author: Maciej Machaczka, Assoc. Prof., e-mail: maciej.machaczka@ki.se

Introduction: After the early successes in therapy of Gaucher disease (GD), allogeneic hematopoietic stem cell transplantation (allo-HSCT) was completely abandoned in developed countries in the 1990s in favor of life-long medical treatment. Here, we report a 30-year follow-up on outcome of Swedish patients with Norrbottnian Gaucher disease type 3 (N-GD3) who underwent allogeneic bone marrow transplantation (allo-BMT) at Karolinska University Hospital between 1982–1991.

Patients and methods: Four patients with N-GD3 underwent allo-BMT. The median age of the patients at the time of transplantation was 2.5 (range 2–9 years). All patients were splenectomized before transplantation. Three patients underwent BMT from related donors and one patient was grafted from an unrelated donor.

Results: All patients engrafted. Two patients developed mild acute GVHD and one patient developed chronic extensive GVHD requiring combined immunosuppressive therapy over many years, until his death from sepsis 7 years after allo-BMT. Two patients are still alive with fully functioning graft after follow-up time of respectively 31 and 27 years. Unfortunately, both of them developed epilepsy after 16 and 22 years after allo-BMT, respectively. Both successfully transplanted patients have normal complete blood counts, no signs of visceral disease as well as skeletal and neurological status fully comparable with other N-GD3 patients receiving ERT. Analysis of plasma chitotriosidase activity (control range: <40 nkat/L) disclosed completely normal levels (10–14 nkat/L) in patients who underwent allo-HSCT as compared with patients treated with ERT (96–1398 nkat/L). One woman with N-GD3 gave birth to a healthy child at the age of 20 years, 18 years after allo-BMT.

Discussion: Our long-time results indicate that Gaucher disease patients can benefit from allo-HSCT. It seems reasonable that, under some circumstances, allo-HSCT could offer a valuable treatment option for Gaucher patients failing medical therapy, as well as for patients suffering from GD3, before development of neurological damage. However, as long as transplant-related mortality of allo-HSCT will not be close to 0% and the risk of GVHD remains significant, it would be questionable to implement allo-HSCT for GD in developed countries, where safe but extremely expensive medical therapy is available for GD patients.

O-02

IMPACT OF LONG TERM ERT IN CHILD. SPANISH EXPERIENCE

Andrade, M.[1,2,3,4] ,Alfonso, P.[2,3], Irún, P.[2,3,5] ,Dalmau, J.[6], Barbera, J.L.[7], Cano, H.[8], Fernandez-Galán, M.A.[9], Franco, R.[10], Gracia, I.[11], Ibañez, A.[12], Lendines, F.[13], Martin-Hernández, E.[14], Pérez del Soto, A.[15], Pérez-Calvo, J.I.[16], Sancho-Val, I.[17], Sanjurjo, P.[18], Pocovi, M.[2,3,5,19] , Giraldo, P.[1,2,3,19]

[1]Haematology Department, Miguel Servet University Hospital, Zaragoza; [2]CIBER de Enfermedades Raras (CIBERER); [3]Aragon Institute of Health Sciences (IACS), Zaragoza, Spain; [4]Rio Hortega Researcher; [5]Biochemistry and Molecular and Cellular Biology Department, Zaragoza University, Zaragoza; [6]Pediatric Department, La Fe University Hospital. Valencia; [7]Pediatric Department Manises Hospital, Valencia; [8]Haematology Department, Los Arcos del Mar Menor University Hospital, Murcia; [9]Haematology Department, Virgen del Puerto Plasencia; [10]Haematology Department, Punta Europa Hospital, Cádiz; [11]Pediatric Department, Miguel Servet University Hospital, Zaragoza; [12]Pediatric Department Rafael Méndez Hospital, Murcia; [13]Pediatric Department, Torrecárdenas Hospital, Almeria; [14]Pediatric Department 12 Octubre University Hospital, Madrid; [15]Haematology Department, Virgen del Rocío University Hospital, Sevilla; [16]Internal Medicine, Lozano Blesa University Hospital, Zaragoza; [17]Haematology Department, Alcañiz Hospital, Teruel; [18]Pediatric Department Cruces University Hospital, Bilbao; [19]Spanish Foundation for the Study and Therapy of Gaucher Disease (FEETEG)

Enzymatic replacement therapy (ERT) had modified the natural history of Gaucher disease (GD). Historically the GD patients had growth retardation; frequently spleen removal, and multiple bone complications. Nowadays we have learnt through clinical trials that patients treated regularly with ERT during childhood achieve a normal percentile of growing and avoid complications. In this report we are summarizing the Spanish experience in the last two decades treating children with GD.

A total of 79 patients diagnosed < 18 years old, 26 of them GD2; 13 developed a GD3 during follow-up and 40 GD1. For the analysis we have included GD1 and GD3 patients. Mean age at diagnosis 5.8 y.o. (range 0.5-17), mean years on therapy 13.2 (2-21), L444P/L444P most frequent genotype in GD3 and N370S/L444P in GD1, 18 females and 35 males, Three patients were splenectomised before diagnosis. The mean on follow-up: 13 y (2-21), 45 received ERT. In first line: Alglucerase 4(8.9%) Imiglucerase (34, 75.5%), Velaglucerase (6.7%) and Taliglucerase (8.9%) 21 patients had received ERT during 15 or more years (15-21), 12 > 10 years (12-14) and 11< 10 years (2-9). Events related to therapy: infusion reactions 2; abandonment 2; changes of ERT, 7; related to disease: growth retardation 5; bone crisis 3; joint replacement 1, osteopenia 2, decreased of coagulation factors (VW,FV,FIX,FXI), others: early diabetes 1, early menarche 1, thyroiditis 1, pregnancies 3, lost follow-up 4. Early onset of therapy in childhood improves long term outcomes in GD. A detailed analysis will be present in the meeting.

O-03

SPINAL DEFORMITIES IN NORRBOTTNIAN TYPE 3 GAUCHER DISEASE: PREVALENCE, POSSIBLE ETIOLOGY, AND MANAGEMENT OPTIONS

Lebel, E.[1†], Kämpe Björkvall, C.[2], Nilsson, M.[3], Klimkowska, M.[4], Myhr-Eriksson, K.[2], Elstein, D.[5], Svenningsson, P.[67], Machaczka, M. [8,9]

[1]Department of Orthopedic Surgery, Shaare Zedek Medical Center, Jerusalem, Israel; [2]Department of Medicine, Sunderby Regional Hospital of Norrbotten County, Luleå, Sweden; [3]Department of Pediatrics, Sunderby Regional Hospital of Norrbotten County, Luleå, Sweden; [4]Department of Clinical Pathology and Cytology, Karolinska University Hospital Huddinge, Stockholm, Sweden; [5]Gaucher Clinic, Shaare Zedek Medical Center, Jerusalem, Israel; [6]Center for Allogeneic Stem Cell Transplantation, [4]Department of Neurology, Karolinska University Hospital Huddinge, Stockholm, Sweden; [7]Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden; [8]Hematology Center Karolinska, Karolinska University Hospital Huddinge; [9]Department of Medicine at Huddinge, Karolinska Institutet, Stockholm, Sweden; †Presenting author: Ehud Lebel MD, PhD, e-mail: lebel@szmc.org.il

Background: Type 3 Gaucher disease among Norrbottnian patients (L444P/L444P) invariably is uniformly expressed as slow neurological progression and a typical spinal deformation. Osteoporosis-related vertebral collapse had been assumed to be the cause of the deformity, and since survival was circumscribed, intervention was not prioritized. This study was designed to define the prevalence, etiology and possible management of spinal deformation in the era of increased longevity because of decades of enzyme replacement therapy (ERT).

Patients and methods: All fifteen patients currently followed at the Sunderby Regional Hospital of Norrbotten County in Luleå, Sweden were invited to be evaluated by an experienced orthopedic surgeon. These patients reside in the Northern Sweden and possibly related to a founder.

Results: There are 8 females and 7 males (aged 4-61 years, one recently died). All receive ERT (30–70 units/kg/infusion every other week); median exposure: 17 (range: 3–17) years. Nine had undergone total splenectomy at a median age of 7 (range: 1–20) years; 7 patients have epilepsy; 2 patients underwent allogeneic bone marrow transplantation at an early age. All patients >3 years have oculomotor apraxia; among older patients severe dystonia is common. Kyphosis and/or kypho-scoliosis was seen in all patients ranging from 30° (in 2/15 patients) to >90° (5/15 patients). Activities of Daily Living (ADL) results were correlated to neurological status, but spinal deformity adversely impacted independence. Three patients had spinal surgery that halted spinal deterioration. Radiological evaluation revealed only mild vertebral wedging/collapse.

Discussion: Deteriorating spinal deformity despite ERT and consequent loss of functionality are probably related to progressive loss of spinal muscular-control and not a result of osteoporosis-related vertebral collapse. Appropriate spinal intervention at an early stage may preserve respiratory function, posture, and possibly ADL.

O-04

CHRONIC NEURONOPATHIC GAUCHER DISEASE: OUTCOMES, MORBIDITY AND MORTALITY IN THE MAINZ COHORT

Mengel, E., Arndt, J., Brixius-Huth, M., Bremova, T., Naumann, S. and Reinke, J.

MC Johannes-Gutenberg-University Mainz, Villa Metabolica in the Center of Pediatric and Adolescence Medicine

As there are new therapeutic options for GD type III on the horizon, natural history studies are important to identify outcome measures and study endpoints. Outcomes, morbidity and mortality were studied in 30 patients aged 3 to 44 years from 1994 to 2014.

During study period 9 patients deceased. In 6 patients mortality was related to neurological symptoms, however 3 patients died due to avoidable visceral reasons. Cognitive decline was evident in 5 patients with myoclonic encephalopathy. In contrast to 25 patients without myoclonic encephalopathy 6 had no cognitive deficits, moreover one patient is aspiring high school degree.

In 6 patients skeletal trunk abnormalities at birth were documented in the medical history. 2 patients developed severe kyphoscoliosis requiring surgery. 1 patient suffered from protein-losing enteropathy and pulmonary involvement successfully treated with eliglustat and ERT.

Abnormal saccadic eye movements were detected in all patients by optokinetic nystagmus testing. However decreased peak velocity was not found in 2 patients with adult manifestation.

Patients and families were asked, what is the most important neurological function which should be improved by treatment? Almost all vote for motor function as it stands for independency and participation in social life.

Morbidity and mortality in neuronopathic GD is based on visceral and neurological signs, which may not be treated with ERT. Motor function tests should be evaluated for endpoints in therapeutic trials.

O-05

THE IMPACT OF ERT ON IMMUNITY IN GAUCHER DISEASE

Komlodi-Pazstor,E.[1], Limgala, R.[1], Martin, C.[1], Hebert, A.[1], Brown, M.[2], Plassmeyer, M.[2], Ryherd, M.[2], Austin, L.[2], Alpan, O.[2], and Goker-Alpan, O.[1]

[1]Lysosomal Disorders Treatment Unit, Fairfax, VA, USA; [2] Amerimmune, Fairfax, VA, USA

Background: Animal models of Gaucher disease (GD) exhibit alterations of the immune system. Similarly, patients with GD often present with abnormalities in the immune response that may be the result of deficiency in cellular and/or humoral immunity.

Cases and Methods: In a prospective study (NCT01358188), the impact of ERT on the immunity was assessed**.** 27 GD patients (19F/8M, mean age 40.2y), 5 were treatment-naïve, were included. Flow cytometry-based immunophenotyping was performed on PBMCs from samples obtained before and after ERT administration, and at indicated intervals. Lymphocyte subpopulations, memory, T-helper, T-killer, NK, B and dendritic cell populations were assayed along with chemokine receptors and activation markers.

Results: At baseline, prior to commencing ERT, CD4/CD8 was low, and transitional B-cells (characterized by CD21 dim expression) were significantly elevated indicating B-cell maturation defect. After establishment of stable-dose therapy, not only the CD4/CD8 ratio was normalized, but also CD21dim-cells were normalized, indicating improved B cell maturation. An increase in dendritic cells was observed. Although the majority of subjects on long-term ERT exhibited normal ranges of lymphocyte subsets, in less than 20%, all of whom were diagnosed before the advent of ERT, CD8 T-cell fraction was either elevated or expressed increased chemokine receptors like CXCR3, CCR6.

Conclusions: Patients with GD present with abnormalities of T and B cells, and other elements of immunity, ERT may correct some of these defects, suggesting the role of therapy on long-term outcome, extending beyond its effects decreasing organ size and improvement of hematological parameters.

O-06

MONOCYTE DYSFUNCTIONAL MIGRATION IN GAUCHER'S DISEASE

Bettman, N.[1*], Katz, T.[1*], Avivi, I.[1,2], Chen Zion, Y.[1], Rosenbaum, H.[1,2]

[1]Department of Hematology & Bone Marrow Transplantation, Rambam Health Care Campus, Haifa, Israel [2]Bruce Rappaport Faculty of Medicine, Technion, Israel Institute of Technology, Haifa, Israel

Introduction: Gaucher's disease (GD) is characterized by glucocerebroside accumulation resulting from an impaired function of the glucocerebrosidase enzyme. This accumulation presumably hampers cell activity, especially in cells exerting high glucocerebrosidase activity such as monocytes. As monocytes activate and regulate innate and adaptive immune functions, their function in GD patients may be impaired.

Aim: To explore the immune system importance in GD etiology.

Methods: Monocytes of untreated GD patients and healthy volunteers (HVs) were tested for their migration capacity towards stromal cell-derived factor 1α (SDF1α). Detailed immuno-phenotypic, functional and molecular analysis followed.

Results: GD patients were found to exhibit reduced numbers of monocytes and demonstrated a defective SDF1α-dependent monocyte migration. Evaluation of the CXC-motif chemokine receptor 4 (CXCR4; SDF1α receptor) expression, revealed its decreased expression on the surface of GD-derived monocytes, while the SDF1α-CXCR4 binding, the CXCR4 internalization and its transcription were found similar in both HVs' and GD patients' monocytes. The reduction in cell-surfaced CXCR4 was accompanied by its increased intracellular expression in patients' monocytes. This reflects the significant elevation in SDF1α concentrations we found in these patients' serum and the lysosomal impairment of GD, which decreases the receptor degradation. Interestingly, a positive correlation of serum SDF1α concentrations and platelets counts seems to exist in GD patients.

Conclusions: GD patients' monocytes exhibit quantitative and functional impairments such as decreased migration capacity towards SDF1α. Patients' serum elevated SDF1α levels may account for this impairment by differentially distributing the expression of CXCR4. Considering SDF1α effect on platelets, its increased levels might ameliorate platelets counts in GD patients. Collectively, the results indicate that various immune-related factors, such as SDF1α, potentially influence GD etiology.

* Equal contributors. Supported by the Gaucher Generation Grant, Genzyme Corporation

O-07

ABERRANT DIFFERENTIATION AND IMPAIRED LYSOSOMAL FUNCTIONS REVEALED BY GAUCHER-SPECIFIC INDUCED PLURIPOTENT STEM CELLS (iPSC)

Panicker, L.M., Sgambato, J.A., Awad, O., Miller, D. and Feldman, R.A.

Department of Microbiology and Immunology, University of Maryland School of Medicine, Baltimore MD, 21201, USA

To model Gaucher disease (GD) we generated iPSC from fibroblasts of patients with types 1, 2 and 3 GD, by expression of the 4 Yamanaka factors (Oct4, Sox2, Klf4 and c-Myc). Directed differentiation of GD iPSC to cell types affected by GD revealed developmental and lysosomal functional abnormalities. GD iPSC-derived macrophages had a striking defect in their ability to clear phagocytosed RBC, recapitulating a characteristic hallmark of GD. GD iPSC macrophages were constitutively activated and produced elevated levels of TNF-alpha, IL-1beta and IL-6, which may increase the risk of developing multiple myeloma. These functional abnormalities were more pronounced in types 2 and 3 than in type 1 GD macrophages. The abnormal phenotypes we observed were reversed by incubation with recombinant glucocerebrosidase or small molecules, to an extent that reflected their known clinical efficacies. Differentiation of GD iPSC to $CD34^{+}CD45^{+}CD43^{+}$ hematopoietic progenitor cells (HPC) was normal, but further differentiation to erythroid and megakaryocytic lineages was compromised, and there was also aberrant myeloid differentiation. These abnormalities were reversed by incubation with recombinant glucocerebrosidase, demonstrating that the phenotypes observed were due to glucocerebrosidase deficiency. GD iPSC-derived osteoblasts also showed developmental abnormalities, and lysosomal functions were compromised. Directed differentiation of GD iPSC to neurons showed that the mutant neurons had autophagy and lysosomal defects that were reversed by recombinant glucocerebrosidase, and will be presented. In sum, patient-derived iPSC provide a very relevant experimental system to elucidate the molecular mechanisms that underlie the pathophysiology of GD, and will have an impact on therapeutic development.

O-08

A ROLE FOR GBA2 IN NEUROPATHOLOGY IN NIEMANN-PICK TYPE C

Marques, A.R.A.[1], Aten, J.[2], Ottenhoff, R.[1], van Roomen, C.P.A.A.[1], Claessen, N.[2], Mirzaian, M.[1], Boot, R.G.[1], Yildiz, Y.[3], Overkleeft, H.S. [4], Aerts, J.M.F.G.[1,4]

[1]Department of Medical Biochemistry and [2]Department of Pathology, Academic Medical Center, Amsterdam, The Netherlands. [3]Department of Internal Medicine, University of Bonn, Bonn, Germany.[4]Leiden Institute of Chemistry, Leiden University, Leiden, The Netherlands

Niemann-Pick type C (NPC) is a neurodegenerative disorder caused by loss-of-function mutations in either the *Npc1* or *Npc2* gene. Within lysosomes, NPC1 and NPC2 proteins are required for the export of cholesterol to other intracellular compartments. NPC patients develop ataxic gait, motor dysfunction and seizures for poorly understood reasons. The neurological symptoms are thought to be related with the cerebral accumulation of glycosphingolipids (GSLs), most prominently gangliosides. The degradation of glucosylceramide (GlcCer) by the lysosomal glucocerebrosidase (GBA1) is known to be impaired in NPC organs and fibroblasts[1,2]. Neuronal cells contain besides GBA1 also the non-lysosomal β-glucosidase (GBA2), which hydrolyses GlcCer to ceramide in the cytosol. During deficiency of GBA1, compensatory GBA2 activity in specific neurons might cause toxic concentrations of ceramide, a pro-apototic lipid[3]. *Npc1*$^{-/-}$ mice treated with a low nanomolar GBA2 inhibitor, N-(5'-adamantane-1'-yl-methoxy)-pentyl-1-deoxynojirimycin (AMP-DNM), show improved motor coordination and an increased lifespan by about 30%. To confirm the neuropathological action of excessive GBA2 activity, we introduced GBA2 deficiency in *Npc1*$^{-/-}$ mice and compared this to the effect of two distinct GBA2 inhibitors. We show that motor coordination and lifespan of *Npc1*$^{-/-}$ mice comparably improve when GBA2 is either pharmacologically inhibited or genetically deficient. The combined findings suggest an important role for GBA2 in NPC neuropathology.

REFERENCES

1. Pentchev, P. G. *et al.* A lysosomal storage disorder in mice characterized by a dual deficiency of sphingomyelinase and glucocerebrosidase. *Biochimica et biophysica acta* **619**, 669–79 (1980).
2. Salvioli, R. *et al.* Glucosylceramidase mass and subcellular localization are modulated by cholesterol in Niemann-Pick disease type C. *The Journal of biological chemistry* **279**, 17674–80 (2004).
3. Haimovitz-Friedman, A., Kolesnick, R. N. & Fuks, Z. Ceramide signaling in apoptosis. *British medical bulletin* **53**, 539–53 (1997).

O-09

SYSTEM-WIDE INVOLVEMENT IN GAUCHER DISEASE: ROLE OF GBA2 AND DOWNSTREAM BIOACTIVE LIPIDS

Mistry, P.K., Yale School of Medicine, New Haven, Connecticut, USA

INTRODUCTION: Inherited deficiency of lysosomal acid β-glucosidase due to biallelic mutations in *GBA1* leads to a multisystemic phenotype of Gaucher disease (GD). There is wide phenotypic diversity among patients harboring identical GBA genotypes and the molecular pathogenesis from substrate accumulation to the clinical phenotype is not understood. Building on the discovery of GBA2 by the Aerts lab (van Weely et al, BBA, 1993, Boot et al, 2007, Yildiz et al, JCI, 2006) Professor Milan Elleder posited extralysosomal transfer of stored lipids and a potential role of GBA2 at the 2006 EWGGD meeting in Cambridge.

RESULTS: We recapitulated the phenotype of human GD through the conditional deletion of *Gba* in *Mx1-Cre*$^{+}$:GD1 mice. There was massive organomegaly but the accumulating substrates represent <1% of the weight of the organs. There was system-wide involvement beyond the macrophage system. The Gaucher cell/macrophage system is the epicenter of the disease responsible for generation of bioactive lipids that engage the cells of the immune system and the bone in disease pathophysiology. Thus there is hypercytokinemia that reflect involvement of the innate as well as the adaptive immune system. We have further shown an array of immune defects in GD1 mice, including defects in early T-cell maturation, B-cell recruitment, and antigen presentation. Concomitantly, there is massive elevation of tissue glucosylceramide (GL1) and glucosylsphingosine (Lyso GL1). The deletion of *Gba2,* the gene encoding neutral glucocerebrosidase, rescued, the GD1 clinical phenotype, despite further elevations in GL-1 and LysoGL-1. This suggests a role for downstream bioactive lipids rather than GL-1 or LysoGL-1 in pathophysiology. Direct testing revealed a strong inhibition of osteoblast viability at nanomolar concentrations of sphingosine, but not with ceramide. This is consistent with high circulating sphingosine levels in GD1 patients, which decline upon imiglucerase enzyme replacement therapy. Serum ceramide levels remain unchanged.

CONCLUSION: Taken together, complementary results from mice and humans affected with GD1 not only pin point sphingosine as being an osteoblast toxin, but also set forth Gba2 as a promising therapeutic target for the future development of inhibitors to ameliorate certain disabling consequences of GD1 and yield promising lipid biomarkers for further validation.

Key words: GBA1, GBA2, glucosylceramide, glucosylsphingosine, sphingosine

O-10

GLYCOLIPID ANORMALITIES IN GAUCHER DISEASE: IS THERE MORE TO LEARN?

Aerts, H.

Department of Medical Biochemistry, Academic Medical Center Amsterdam

For almost hundred years, attention has been focused on the intralysosomal deposition of glucosylceramide (GlcCer) in macrophages of Gaucher patients. Evidence will be presented that in Gaucher disease there are additional abnormalities in glycolipids beyond those in GlcCer. Well documented already are the elevations in gangliosides and glycosyl sphingosine, i.e. deacylated GlcCer, in Gaucher patients. The potential (patho) physiological consequences of these abnormalities are discussed. Attention is also paid to their value in diagnosis and therapy monitoring.
The availability of smart substrate analogues and ultrasensitive LC- MS metabolomics has led to the very recent identification of other abnormal glycolipids with impact on cholesterol metabolism. The implication of these new findings for better understanding of some aspects of Gaucher disease as well as therapy approaches is addressed.
Note: The unpublished work has been conducted by many collaborators in the Department of Medical Biochemistry (AMC) and the Department of Bio-organic Synthesis at the Leiden Institute of Chemistry.

O-11

UNUSUAL PRESENTATIONS OF GAUCHER DISEASE

Rosenbaum, H.

Department of Hematology and Bone Marrow Transplantation Rambam Medical Center, Bruce Rappaport Faculty of Medicine, Technion, Haifa, Israel

Case 1: 39 y old male presented with purpura, throbocytopenia and hepatosplenomegaly. Megakariocyte hyperplastia and Gaucher cells were detected in bone marrow (BM). Gaucher disease (GD) was diagnosed with low glucocerebrosidase and 84GG/1604 mutation. The BM findings and presence of IGG platelet antibodies suggested the diagnosis of immne trombocytopenia. Enzyme replacement (ERT), steroids, IVIG and Rituximab resulted in decrease of liver and spleen volumes with short response regarding bleeding and platelet count. Romiplostim increased platelet count. Hip AVN was diagnosed, the etiology will be discussed.

Case 2: 59 y old GD patient with mild course diagnosed with colon carcinoma. Splenomegaly and severe thrombocytopenia were found with no bleeding phenomena. Bone marrow showed massive infiltration by Gaucher cells. Platelet antibodies were not detected. Chemotherapy was postponed because of severe thrombocytopenia. ERT resulted in decrease of splenic volume with persistent severe thrombocytopenia. Hypo ecchogenic lesions in the liver raised the question of infarcts or metastasis. Liver biopsy confirmed metastatic disease. Due to persistent thrombocytopenia embolisation of the splenic artery was performed succefully. Incsreased platelet count enabled chemotherapy.

Case 3: 78 y old diagnosed at age 58 with GD and underwent partiel splenectomy.
Followed 20 y with pancytopenia and monoclonal gammopathy with no ERT. He was admitted to our clinic with Plasma cell leukemia, splenomegaly and renal failure. ERT, Bortezomib+Cytoxan+Dexacort resulted in very good partial remission enabaling institution of Lenalidomide as maitanance.

Case 4: 66 y old GD patient suffered from long course of relapsing Waldenstrom Macroglobulinemia. Remissions were achieved by combining chemotherapy, Rituximab and ERT. He died because of metastatic renal cell carcinoma and myelodysplastic syndrome with no evidence of GD in the bone marrow.

O-12

THE PREVALENCE OF GAUCHER IN IDIOPATHIC SPLENOMEGALY IS 1.50: FOLLOW-UP OF A NATIONWIDE SCREENING STUDY IN 200 PATIENTS

vom Dahl, S.[1], Bange, M.[2], Merkel, M.[3], Voßbeck, J.[4], Mengel, E.[5], Herrmann, A.[2], Donner, M.[1], Santosa, D.[1], Häussinger, D.[1]

[1]Department of Gastroenterology, Hepatology and Infectious Diseases, University of Düsseldorf, Moorenstrasse 5, D-40225 Düsseldorf, Germany; [2]Dept. of Internal Medicine/Gastroenterology, St. Franziskus-Hospital, Köln, Germany; [3]Dept. of Internal Medicine, Diabetes, Gastroenterology, Endocrinology and Metabolic Diseases, Asklepios-Klinik St. Georg, Hamburg, Germany; [4]Dept. of Pediatrics, Universitätsklinikum Ulm, Germany; [5]Zentrum für Kinder- und Jugendmedizin, Villa Metabolica, Johannes-Gutenberg-University, Mainz, Germany

Background: The incidence of GD in newborns is about 1:40.000. There is a discrepancy between the predicted and known cases of GD in Germany (300 known vs. 1500-2000 predicted patients in Germany). Splenomegaly is a compulsory symptom in visceral Gaucher disease, but the pathognomic Gaucher cells may not be found in bone marrow smears. **Aim:** To determine the prevalence of GD in patients with idiopathic splenomegaly. **Methods:** In cooperation with hematooncologists in Germany, □-glucocerebrosidase (GBA) and chitotriosidase (CT) activities were primarily determined in blood samples from patients who presented with idiopathic splenomegaly of unknown origin. Common hematooncologic, hepatic, infectious or autoimmune causes had been excluded. A physician-based questionnaire determined biographic data, hepatosplenomegaly, thrombocytopenia and anemia. Follow-up with clinical data from the diagnosed patients was recovered from the 9 German Gaucher treatment centers. **Results:** From 2008 to 2012 a total of 200 samples was analysed for GBA and chitotriosidase activity. 59% were male, age range was 0-88 years. Splenomegaly was present in 85%, severe splenomegaly in 34%. Hepatomegaly was present in 46%, 57% of all analysed patients had low platelets, 40% were anemic. In 74% of all patients, lymphoma, leucemia, multiple myeloma oder severe infection had been properly excluded. Out of 200 patients, four patients had pathological GBA acticity, three with increased CT activity (Tab. 1).

m / w	Age	Symptoms/findings	GBA activity (Ref.: 20-70 pmol/min/mg)	CT activity (Ref.: < 1,5 nmol/min/ml)	Bone marrow biopsy
m	11 d	Icterus, splenomegaly, thrombocytopenia	3,9	19,7	negative
w	21 ys.	thrombocytopenia, hepatosplenomegaly	7,0	0,1*	not done
m	45 J.	thrombocytopenia, splenomegaly, bone pains	10,0	20,0	positive
w	43 J.	thrombocytopenia, hepatosplenomegaly	10,0	18,7	positive

Tab. 1: Clinical and laboratory findings in the 4 diagnosed GD patients: *, chitotriosidase null mutation GBA: □-Glucocerebrosidase; CT: Chitotriosidase.

Discussion: In 4 out of 200 with idiopathic splenomegaly, M. Gaucher was found. The predicted prevalence in this cohort is estimated to be 1:50. Facing the good therapeutic options and the need for early diagnosis, lab testing, preferably by DBS, is recommended in patients with etiologically unclear splenomegaly.

O-13

HIGH PREVALENCE OF SMALL FIBRE NEUROPATHY IN TYPE 1 GAUCHER DISEASE

Devigili, G.*, Ciana, G.°, Sechi, A.°, Deroma, L.°, Dardis, A.°, Zampieri, S.°, Deganuto, M.°, Cattarossi, S.°, Pianta, A.°, De Filippo, M.°, Lettieri, C.*, Rinaldo, S.*, Eleopra, R.*, Bembi, B.°

*Neurology Department, Academic Hospital of Udine, Udine, Italy
°Regional Coordinator Centre for Rare Diseases, Academic Hospital of Udine, Udine, Italy

Background: pain is a disabling symptom in GD1 generally described as secondary to bone involvement. Recently an increased frequency of peripheral neuropathy has also been described in GD1. In our clinical practice we have observed the persistence of legs pain in a group of GD1 patients receiving long-term ERT.

Aim of the study: to investigate the origin and characteristics of persisting pain and in a cohort of GD 1 patients.

Patients and Methods: 25 adult GD1 patients (13 females, 12 males; 23 on ERT >10 years, 2 untreated) were studied. Retrospective clinical history was collected from patient records. Comorbidity for peripheral neuropathy was excluded. Neuropathic pain features were assessed by Douleur Neuropathique in 4 questionnaires (DN4), Neuropathic Pain Symptom Inventory (NPSI), Quantitative Sensory Testing (QST) and skin biopsy with quantification of intraepidermal nerve fibres at distal leg and proximal thigh.

Results: 12/25 patients complained about chronic pain. None suffered bone crisis during the last year. All 12 patients complain painful sensation suggestive of neurotic pain features with proximal patchy distribution (6 presented pain paroxysmal). Epidermal denervation was observed on skin biopsy of 20/21 patients (included the 2 untreated patients). QST showed the presence of high thermal threshold with wrong cold sensation, paradoxical heat sensation and increased mechanical detection thresholds. Nerve conduction studies were negative.

Conclusions: clinical symptoms and tests results are consistent with a diagnosis of small fiber neuropathy (SFN). These data described for the first time the high prevalence of SFN in GD1.

O-14

WHOLE-BODY MRI IRON LEVEL MEASUREMENT IN GAUCHER DISEASE

Regenboog, M.[1–2], Akkerman, E.M.[2], Stoker, J.[2], Hollak, C.E.M.[1]

[1]Department of Endocrinology and Metabolism, Academic Medical Center, University of Amsterdam, The Netherlands; [2]Department of Radiology, Academic Medical Center, University of Amsterdam, The Netherlands.

Introduction: Residual disease burden in Gaucher disease (GD) may be related to the occurrence of late complications or associated conditions. Currently, no imaging modality is available that quantifies the residual disease burden and reflects the different storage compartments in GD. Iron can be found in Gaucher cells and therefore it is possible that remaining depots of iron in the body could be used as a marker of residual disease. With whole-body MRI iron level measurement, we introduce a novel approach to evaluate residual disease activity.

Methods: MRI images are obtained using a 1.5T-scanner. We determine T2* measurements for abdominal viscera, bone marrow and heart. R2* values (inversely proportional to T2*, correlation with iron concentration) are reported as mean of a region of interest (ROI) of each site studied. A colour scale is used. The first GD patient (female, age 70, splenectomized) is included and compared to a healthy control (female, age 28).

Results: differences in R2* values between the GD patient and healthy control are observed. A prominent difference is seen in the liver: mean R2* over ROI is 164 Hz for the GD-patient and 37 Hz for the healthy control. Other iron storage sites include spine, pelvis and femora. More results are collected and can be presented at the meeting.

Discussion: our findings indicate signs of iron storage in locations typical for GD. The investigations will focus on the pattern of distribution of residual Gaucher cell depots in relation to disease severity, specific disease markers and occurrence of complications.

O-15

PREVALENCE OF AUTOANTIBODIES IN THE COURSE OF GAUCHER DISEASE TYPE 1

Serratrice, C.[1], Bensalah, N.[2], Belmatoug, N.[3], Masseau, A.[4], Rose, C.[5], Kaminsky, P.[6], Lidove, O.[7], Camou, F.[8], Maillot, F.[9], Leguy Seguin, V.[10], Bertrand, N.M.[11], Marie, I.[12], Cabane, J.[13], Alessandrini, M.[14], Bardin, N.[2], Boucraut, J.[2], Berger, M.[15]

[(1)]Department of internal Medicine, Foundation Hospital Saint Joseph, Marseille, France, [(2)]Laboratory of immunology, CHU Conception, Marseille [(3)]Referal Center for Lysosomal Diseases, CHU Paris Nord Val de Seine [(4)]Department of internal Medicine, CHU Hôtel Dieu, Nantes [(5)]Department Onco-Hématology, University Catholique Lille [(6)]Department of internal medicine, Brabois Hospital, Vandoeuvre les Nancy [(7)]Department of internal medicine-Rheumatology, La Croix Saint Simon Hospital, Paris [(8)]Medical Intensive Care Unit, CHU Saint André, Bordeaux [(9)]Department of internal medicine, CHU Tours [(10)]Department of internal Medicine, CHU Dijon [(11)]Department of internal Medicine, CHU Jean Minjoz, Besançon [(12)]Department of internal Medicine, CHU Rouen [(13)]Department of Internal Medicine, Saint-Antoine Hospital, Paris [(14)]EA 3279 Research Unit, Marseille [(15)]Department of hematology, CHU Estaing, Clermont Ferrand, France

Hypergammaglobulinemia is usually observed in Gaucher disease (GD). If monoclonal gammopathy and myeloma are well documented, polyclonal gammopathies are less investigated. Moreover there are few data about auto-immunity in GD patients. Two studies analysing the presence of autoantibodies during GD were reported (1995, 2011). More, cases of GD associated with immune hemolytic anemia, antiphospholipid syndrome, and immune thrombocytopenia were published.

The aim of this study was to determine the prevalence of autoantibodies and autoimmune features in GD, compared with healthy subjects. We evaluated if main GD characteristics were correlated with the presence of autoantibodies.

Patients and methods:

A prospective multi-centre study was performed. Blood samples were forwarded to a single specialized laboratory and were tested for antinuclear, anti ENA, antiphospholipid, and antiganglioside. Main GD characteristics and auto-immune features were collected. This study obtained agreement from an ethical committee and approval by French Data Protection Commission (CNIL).

Results:

Forty patients (18M, 22F) and 20 healthy subjects were included. Fifty two percent had abnormalities on protein electrophoresis. Fifty percent of patients with GD had autoantibodies, instead of 20% in the controls. Fifteen per cent of GD patients had antinuclear (half of them were antiRo-SSa), 27.5% had antiphospholipid and 12.5% had antiganglioside. None of the GD patients had relevant autoimmune disease. We did not evidence correlation between genotype, splenectomy, bone infarcts or osteonecrosis and presence of autoantibodies.

Conclusion:

Autoantibodies are retrieved more frequently in GD, but without features evoking auto-immune disease. We will discuss the mechanisms leading to autoimmunity during GD.

O-16

AN UNSUSPECTED DYSERYTHROPOIESIS IN GAUCHER DISEASE

Reihani, N.[1-4] , Arlet, J.B.[4,8] , Billette de villemeur, T.[5,6] , Belmatoug, N.[5,6] , Colin, Y.[1-4] , Hermine, O.[4,8] , LeVan Kim, C.[1-4] & Franco, M.[1-4]

[1]Inserm U1134, Paris, France; caroline.le-Van-kim@inserm.fr; [2]Université Paris Diderot, Sorbonne Paris Cité, UMR_S 1134, Paris, France; [3]Institut National de la Transfusion Sanguine, Paris, France; [4]Laboratoire d'excellence GR-Ex, Paris, France; [5]Service de Neuropédiatrie, Hôpital Trousseau, Assistance Publique–Hôpitaux de Paris and Université; Pierre et Marie Curie, Paris, France; [6]Centre de Référence des Maladies Lysosomales, Clichy, France; [7]Service de Médecine Interne, Hôpital Beaujon, Clichy, France; [8]CNRS UMR8147 and Service d'Hématologie, Hôpital Necker, Paris, France

Gaucher disease (GD) is a lysosomal storage disorder, impairing glucosylceramide catabolism. GclCer-laden macrophages transform into Gaucher cells and are responsible for the major GD symptoms (tissue infiltration, organomegaly, bone lesion). However, other signs of the disease such as anemia, vascular occlusion, spleen and bone infarcts might involve red blood cells (RBC). Our previous findings uncover an overlooked aspect in GD showing that GD RBC exhibited abnormal rheological and membrane adhesion properties. Thus, RBC could be considered as culprit for ischemic events in GD.

To determine whether GD could affect erythropoiesis leading to abnormal properties of mature RBCs, we induced *in vitro* erythropoiesis from circulating GD patient progenitors.

Methods: After purification of CD34+ from peripheral blood of Gaucher patients (n=20) or controls, erythroid progenitors are expanded in the absence of erythropoietin and differentiated in a second step with erythropoietin. Proliferation as well as erythroid differentiation is examined. Our preliminary results showed: (i) a dramatic decrease in proliferation in the first step of expansion, (ii) an accelerated maturation. (iii) Co-culture experiments suggest that Gaucher macrophages do not affect erythroid terminal maturation.

In conclusion, we evidenced an unexpected dyserythropoiesis characterized by accelerated erythroid differentiation. To decipher the molecular mechanism(s) of this impairment, we are currently investigating if sphingolipids accumulation and/or donwstream bioactive lipids are contributor to dyserythropoiesis.

We expect that these studies may help to understand the role of erythroid cells in the pathophysiology of GD as well as the mechanism of anemia.

This work was supported in part by grants from Shire.

O-17(a)

THE ORIGINS OF GLUCSYLSPHINGOSINE

Ferraz, M.J., Appelman, M.D., Verhoek, M., Strijland, A., Scheij, S., Ouairy, C.*, Boot, R., Aerts J.M.

Department of Medical Biochemistry, Academic Medical Center, University of Amsterdam, Meibergdreef 15, 1105 AZ Amsterdam (The Netherlands); *Bio-organic Synthesis, Leiden Institute of Chemistry, P.O. box 9502, 2300 RA Leiden (The Netherlands)

In Gaucher disease, the deficiency in the lysosomal glucocerebrosidase (GBA1) leads to the accumulation of glucosylceramide. The presence of the secondary metabolite, glucosylsphingosine has also been reported in human Gaucher disease patients and mouse models with reduced GBA1 activity. This metabolite can be used as circulating biomarker for disease severity and is useful to monitor treatment efficacy.

The mechanisms of glucosylsphingosine formation remain unclear. It has been speculated that these lysolipids are formed during *de novo* synthesis and that a deficiency in degradation leads to their accumulation. Our latest results point its origin to the degradation of the primary storage material, glucosylceramide, by acid ceramidase (AC).

AC is a complex lysosomal enzyme consisting of two subunits of the N-terminal nucleophile (ntn) hydrolase family. The active n-terminal cysteine of the enzyme is generated by an auto-proteolytic cleavage step leading to an enzyme that consists of two disulfide linked subunits. AC catalyzes the hydrolysis of ceramide into sphingosine and free fatty acid, one of the final steps in sphingolipid degradation. According with our results and recent literature, AC shows more promiscuous substrate specificity than classically described.

In vivo inhibition of glucocerebrosidase in fibroblasts of Farber disease patients (deficient in AC activity) leads to significantly less glucosylsphingosine production when compared with wild-type fibroblasts. The same results are shown following AC inhibition with Carmofur in the presence of conduritol-β-epoxide (CBE), wild-type fibroblasts accumulated glucosylceramide but failed to produce glucosylsphingosine. Additionally, over-expression of AC in Farber fibroblasts rescues the phenotype. We observed a correction of ceramide levels and glucosylsphingosine production upon GBA1 inhibition with CBE.

Work is in progress to further elucidate the role of acid ceramidase in glucosylsphingosine production by deacylation of the substrate glucosylceramide and the possible mechanism involved.

O-17(b)

LC-MS/MS QUANTIFICATION OF GLUCOSYLSPHINGOSINE IN URINE AND PLASMA OF TYPE 1 GAUCHER PATIENTS USING AN ISOTOPE STANDARD

Mirzaian, M.[1], Wisse, P.[2], Ferraz, M.J.[1], Gold, H.[2], Donker-Koopman, W.E. [1], Verhoek Marri[1], Overkleeft H.S. [2], Boot R.G.[1], Kramer G.[1], Dekker N., Aerts J.M.F.G.[1]

[1]Department of Medical Biochemistry, Academic Medical Centre, Amsterdam, the Netherlands; [2]Leiden Institute of Chemistry, Leiden University, Leiden, the Netherlands

We earlier reported marked increases in deacylated GlcCer, i.e. glucosylsphingosine (GlcSph), in plasma of GD patients. To improve quantification, [5, 6, 7, 8, 9] $^{13}C_5$-GlcSph was synthesized for use as internal standard with quantitative LC-ESI-MS/MS. The method was validated using plasma of 59 GD patients and 20 controls. Intra-assay variation was 1.8% and inter-assay variation 4.9% for GlcSph (m/z 462.3). Plasma GlcSph levels with the old and new methods closely correlate (r = 0.968, slope = 1.038). Next, we analysed GlcSph in 24 h urine samples of 30 GD patients prior to therapy. GlcSph was quantifiable in the patient samples (median 1.20 nM), but was below detection in normal urine. In analogy to globotriaosylsphingosine in urine of Fabry disease patients, multiple isoforms of GlcSph differing in structure of the sphingosine moiety are present in GD urine. Whilst in GD plasma GlcSph with m/z 462.3 is by far the most abundant isoform, in urine of the same patients hydroxylated and poly-unsatured glucosylsphingosines are far more prominent species. Enzyme replacement therapy led to a comparable decrease of various GlcSph isoforms in urine of GD patients, coinciding with reductions in plasma GlcSph and markers of storage macrophages (chitotriosidase and CCL18).

In conclusion, GlcSph can be sensitively detected by LC-ESI-MS/MS with an internal isotope standard. Elevated GlcSph in urine of GD patients is chemically markedly heterogeneous.

O-18

TALIGLUCERASE ALFA IN ADULT PATIENTS WITH GAUCHER DISEASE WHO WERE PREVIOUSLY TREATED WITH IMIGLUCERASE: 36-MONTH SAFETY AND EFFICACY RESULTS

Pastores, G.M.[1], Shankar, S.P. [2], Petakov, M.[3], Giraldo, P. [4], Rosenbaum, H. [5], Amato, D.J. [6], Szer, J. [7], Chertkoff R. [8], Brill-Almon, E. [8], Zimran, A.[9†]

[1]Department of Medicine/National Centre for Inherited Metabolic Disorders Mater Misericordiae University Hospital, Dublin, Ireland; [2]Department of Human Genetics, Emory University School of Medicine, Atlanta, GA, USA; [3]Clinical Center of Serbia, Institute of Endocrinology, Diabetes and Metabolic Diseases, Belgrade, Serbia; [4]Hospital Universitario Miguel Servet, Servicio de Haematologia, Zaragoza, Spain; [5]Rambam Medical Center, Haematology Ambulatory Services, Haifa, Israel; [6]Mount Sinai Hospital, Toronto, Ontario, Canada;[7]Clinical Haematology and Bone Transplant Service, Royal Melbourne Hospital, Victoria, Australia; [8]Protalix Biotherapeutics, Carmiel, Israel; [9]Gaucher Clinic, Shaare Zedek Medical Center, Jerusalem, Israel

†Presenting Author's Contact Information: Ari Zimran, MD; Gaucher Clinic, Shaare Zedek Medical Center; 12 Bayit Street, P.O. Box 3235, Jerusalem 91031, Israel; Tel: 972-509-149149; Fax: 972-2-6517979; azimran@gmail.com

Introduction: Taliglucerase alfa is the first approved plant cell–expressed recombinant human protein and is an enzyme replacement therapy indicated for treatment of adults with Type 1 Gaucher disease (GD). Safety and efficacy were evaluated in adult patients switched from imiglucerase to taliglucerase alfa in study PB-06-002 and extension study PB-06-003.
Aim: To report 36-month safety and efficacy results of taliglucerase alfa treatment of adult patients with GD who were previously treated with imiglucerase.
Methods: Patients with stable disease were switched from a stable dose of imiglucerase to the same dose of taliglucerase alfa given every other week. Spleen volume, liver volume, hemoglobin concentration, platelet counts, and chitotriosidase activity were assessed through 36 months.
Results: Mean (SE) values at baseline and study end were as follows, respectively: spleen volume (n=11), 4.6 (1.2) and3.7 (0.9) multiples of normal (MN); liver volume (n=12), 1.0 (0.1) and1.0 (0.1) MN; hemoglobin concentration (n=14),13.4 (0.4) and 13.3 (0.3) mg/dL; platelet counts (n=15), 171,222 (24,032) and 172,467 (23,067)/mm^3;and chitotriosidase activity (n=10), 12,206 (4,934) and 6,551 (3,018) nmol/ml*hr. All treatment-related adverse events (AEs) were mild/moderate and transient. The most common AEs were nasopharyngitis, arthralgia, upper respiratory tract infection, headache, and pain in extremity.
Discussion: These 36-month results of taliglucerase alfa treatment in adult patients with GD who were previously treated with imiglucerase extend the clinical safety and efficacy data on taliglucerase alfa. Mean disease parameters were similar at baseline and following long-term treatment with taliglucerase alfa, suggesting ongoing disease stability.

Disclosure

This study was sponsored by Protalix Biotherapeutics. Editorial and medical writing support was provided by Peloton Advantage, LLC, and was funded by Pfizer. Pfizer and Protalix entered into an agreement in November 2009 to develop and commercialize taliglucerase alfa.

O-19

PLATELET COUNT AND CHITOTRIOSIDASE ACTIVITY IN PATIENTS WITH TYPE 1 GAUCHER DISEASE WHO WERE SWITCHED FROM IMIGLUCERASE TO VELAGLUCERASE ALFA

Elstein, D.,[1†] Zimran, A.,[1] Hughes, D.A.,[2] Giraldo, P.,[3] Charrow, J.,[4] Smith, L.,[5] Shankar, S.P.,[6] Kunes, Y.,[7] Wang, N.,[7] Dinh, Q.,[7] Crombez, E.,[7] Mehta, A.[2]

[1]Shaare Zedek Medical Center and Hebrew University-Hadassah Medical School, Jerusalem, Israel; [2]Royal Free Hospital and University College London, London, UK; [3]CIBERER and Hospital Universitario Miguel Servet, Zaragoza, Spain; [4]Ann & Robert H. Lurie Children's Hospital, Chicago, IL, USA; [5]Children's Mercy Hospital, Kansas City, MO, USA; [6]Emory University, Atlanta, GA, USA; [7]Shire, Lexington, MA, USA

†Presenting author: Deborah Elstein; Gaucher Clinic, Shaare Zedek Medical Center, Jerusalem, Israel; email: elstein@szmc.org.il

Background: Patients with type 1 Gaucher disease who switched from imiglucerase to velaglucerase alfa were evaluated in a 12-month trial, TKT034, and extension study HGT-GCB-044. Primary and secondary TKT034 endpoint-data are published. A prior publication including imiglucerase-experienced patients who were switched to early-access velaglucerase alfa suggested patients switching to another enzyme therapy may approach near-normal values; a post hoc, exploratory sub-analysis of TKT034-extension data was performed to evaluate this. **Methods:** Within-patient changes in platelets and chitotriosidase activity from entry into TKT034 (Baseline) were assessed specifically as sensitive Gaucher disease markers. **Results:** 38 patients were studied (aged 9-71 years; pre-switch imiglucerase exposure 22-192 months [median 65]; 10-50 months' treatment in extension). 27/30 patients (90%) with normal Baseline platelet counts (≥120×10^9/L) either were stable (≤20% change) or had improved by >20% at the time of the last assessment. 4/8 (50%) who had below-normal platelet counts before switching normalized at a post-Baseline assessment. 75% of the below-normal group (6/8) had a good or moderate response (using Hollak et al.'s definitions, >30×10^9/L or >15×10^9/L increase, though previously applied only to patients with pre-treatment values <100×10^9/L); 0/8 experienced treatment failure (<-15×10^9/L). 21/22 patients (95%) with Baseline chitotriosidase values ≤5000 nmol/mL/h were stable (≤15% change) or had improved (<-15%) at the last assessment. 9/15 (60%) who had Baseline values >5000 saw the measurement decrease to ≤5000 nmol/mL/h at a post-Baseline assessment. **Conclusion**: Platelet and chitotriosidase measurements were stable or improved in almost all 38 patients in these studies switched from long-term imiglucerase. Confirmatory studies are needed.

Disclosure and Funding Statement

DE currently receives reimbursement for travel expenses and honoraria for meetings from Shire. AZ receives consultancy fees from Protalix Biotherapeutics, has options in Protalix Biotherapeutics, and is a member of its Scientific Advisory Board. AZ receives honoraria from Shire and Pfizer, and his institution receives support from Genzyme for participation in the International Collaborative Gaucher Group Gaucher Registry and from Shire for participation in the Gaucher Outcome Survey. DAH has received consultancy fees, travel and research grants, and honoraria for speaking from Shire, Genzyme, Protalix Biotherapeutics, and Amicus. PG has received consultancy fees from Shire, Genzyme, Protalix Biotherapeutics, and Actelion. JC is a member on Advisory Boards for Genzyme, Shire, Pfizer-Protalix Biotherapeutics, BioMarin, and Synageva; receives consultancy or speaker fees from Genzyme, Shire, Pfizer-Protalix Biotherapeutics, BioMarin, and Synageva; and has recently participated in clinical trials sponsored by Genzyme, Shire, Amicus, GSK, and BioMarin. LS has no competing interests to declare. SPS has received honoraria from Shire, Genzyme, and Protalix as a medical investigator and speaker. SPS's institution receives grants for participation in clinical trials and education grants for patients with Gaucher disease from Shire, Genzyme, and Protalix, and participates in the Gaucher Registries and Gaucher Outcome Survey. AM receives consulting fees from Shire and his institution has received unrestricted research grants from Shire. YK, NW, QD, and EC are employees of Shire. DE, AZ, DAH, PG, JC, LS, SPS, and AM were investigators in the clinical trials TKT034 (ClinicalTrials.gov identifier NCT00478647) and HGT-GCB-044 (NCT00635427), which were sponsored by Shire. The authors thank Clare Guni, of Excel Scientific Solutions, who provided medical writing services on behalf of Shire.

O-20

SEVEN-YEAR FOLLOW-UP IN A PHASE I/II TRIAL AND OPEN-LABEL EXTENSION STUDY FOR VELAGLUCERASE ALFA IN TREATMENT-NAÏVE ADULTS WITH TYPE 1 GAUCHER DISEASE

Elstein, D. [1*], Wang, N. [2], Ogg, C. [2], Crombez, E. [2], Cohn, G.M. [2], Zimran, A.[1]

[1]Shaare Zedek Medical Center and Hebrew University-Hadassah Medical School, Jerusalem, Israel;
[2]Shire, Lexington, MA, USA
[*]Presenting author; affiliation: Gaucher Clinic, Shaare Zedek Medical Center, Jerusalem, Israel; correspondence: elstein@szmc.org.il (Deborah Elstein)

Introduction: TKT025EXT was an open-label extension study for patients who completed TKT025, a 9-month, first-in-human trial of velaglucerase alfa in patients ≥18 years old with Gaucher disease type 1 (GD1). TKT025EXT was designed to evaluate velaglucerase alfa's longer-term safety and clinical activity. **Methods:** Patients in TKT025EXT continued every-other-week, intravenous infusions at 60 U/kg. TKT025EXT included options for home therapy and, for patients who achieved ≥2 of 4 therapeutic goals, dose reduction to 30 U/kg. **Results:** Ten patients enrolled and n=8 completed TKT025EXT with 80-89 months' cumulative study-drug exposure (TKT025 included). All patients who completed 15-18 months' cumulative exposure were eligible for and underwent dose reduction. 7/8 patients eligible for home therapy received home infusions. All patients experienced ≥1 adverse event (AE) in TKT025EXT. Two study-drug-related AEs (bone pain, fatigue) occurred in one patient. Bone pain in another patient prompted a dose increase. No patients discontinued due to AEs or developed anti-drug antibodies. Statistically significant mean changes from Baseline (pre-TKT025) were observed in hemoglobin concentration, platelet count, liver and spleen volumes; 8/8 patients had achieved the 5-year therapeutic goals for these variables and bone density 45-48 months from Baseline (bone endpoints were exploratory). For hemoglobin, platelets, and liver volume, most or all patients achieved normalization or near normalization. **Conclusion:** Velaglucerase alfa was generally well tolerated. Key clinical parameters improved in all patients. Normalization or near normalization of clinical variables, in a setting of dose reduction and home therapy, suggests higher therapeutic expectations could be considered for GD1 patients receiving enzyme replacement.

Disclosure and Funding Statement
DE currently receives reimbursement for travel expenses and honoraria for meetings from Shire. AZ receives consultancy fees from Protalix Biotherapeutics, has options in Protalix Biotherapeutics, and is a member of its Scientific Advisory Board. AZ receives honoraria from Shire and Pfizer, and his institution receives support from Genzyme for participation in the International Collaborative Gaucher Group Gaucher Registry and from Shire for participation in the Gaucher Outcome Survey. NW, CO, EC, and GMC are employees of Shire. DE and AZ were investigators in the clinical trials TKT025 and TKT025EXT (ClinicalTrials.gov identifier NCT00391625), which were sponsored by Shire. The authors thank Clare Guni, of Excel Scientific Solutions, who provided medical writing services on behalf of Shire.

O-21

THE UPR-ASSOCIATED TRANSCRIPTION FACTOR CHOP UPREGULATES EXPRESSION OF THE GBA GENE

Maor, G., Braunstein, H. and Horowitz, M.

Department of Cell Research and Immunology, Tel Aviv University, 69978, Israel

Inability to properly fold misfolded proteins and their retention in the ER leads to ER stress, which mediates unfolded protein response (UPR) and ER Associated Degradation (ERAD).
We have previously shown that UPR is activated in cells that derived from GD patients and in cells carrying GD mutations. This UPR results in activation of the transcription factors CHOP and Xbp1.
We have shown in the past that GBA mRNA level increases in GD derived cells in comparison to non-GD cells [1]. Employing quantitative RT-PCR we could confirm that GBA transcription is elevated not only in GD derived cells, but also in cells carrying different GD mutations. In light of UPR activation in GD derived cells and cells carrying different GD mutations, we wondered whether this upregulation is mediated by UPR-activated transcription factors like CHOP. A bioinformatics search, using the TransFac database, revealed that the GBA promoter contains a CHOP binding site.
In order to test a possible effect of CHOP on transcription of the GBA promoter, the latter was coupled to the luciferase expressing gene and its activity was measured in cells, in the presence or absence of CHOP expression. Our results showed that the normal, but not a GBA promoter mutated in its CHOP binding site, was activated by CHOP, as measured by luciferase activity.
Our results strongly imply that UPR activation in GD derived cells and in cells carrying different GD mutations results in induction of GBA transcription, mediated by the transcription factor CHOP.

REFERENCES

1. Reiner, O. and M. Horowitz, *Differential expression of the human glucocerebrosidase-coding gene.* Gene, 1988. **73**(2): p. 469-78.

O-22

TALIGLUCERASE ALFA 36-MONTH CLINICAL SAFETY AND EFFICACY IN TREATMENT-NAÏVE PATIENTS

Zimran, A.[1†], Durán, G.[2], Mehta, A.[3], Giraldo, P.[4], Rosenbaum, H.[5], Giona, F.[6], Amato, D.J.[7], Petakov, M.[8], Terreros Muñoz, E.[9], Solorio-Meza, S.E.[10], Cooper, P.A.[11], Chertkoff, R.[12], Brill-Almon, E.[12]

[1] Gaucher Clinic, Shaare Zedek Medical Center, Jerusalem, Israel, and the Hadassah Medical School - Hebrew University, Jerusalem, Israel; [2]Pontificia Universidad Catolica de Chile, Division de Pediatria, Santiago, Chile; [3]Royal Free and University College School of Medicine, Department of Haematology, Royal Free Hospital, London, UK; [4]Hospital Universitario Miguel Servet, Servicio de Haematologia CIBER de Enfermedades Raras (CIBERER), Zaragoza, Spain; [5]Department of Hematology, Rambam Medical Center, Haifa, Israel; [6]"Sapienza" University, Department of Cellular Biotechnologies and Hematology, Hematology Section, Rome, Italy; [7]Mount Sinai Hospital, Toronto, Ontario, Canada; [8]Clinical Center of Serbia, Institute of Endocrinology, Diabetes and Metabolic Disease, Belgrade, Serbia; [9]Centro Médico Nacional Siglo XXI, Servicio de Hematologia, México City, México; [10]Hospital de Especialidades No. 1, Unidad de Investigacion, colonia Los Paraisos, Leon Guanajuato, Mexico; [11]University of the Witwatersrand & Charlotte Maxeke Johannesburg Academic Hospital, Johannesburg, South Africa; [12]Protalix Biotherapeutics, Carmiel, Israel

†Presenting Author's Contact Information: Ari Zimran, MD; Gaucher Clinic, Shaare Zedek Medical Center; 12 Bayit Street, P.O. Box 3235, Jerusalem 91031, Israel; Tel: 972-509-149149; Fax: 972-2-6517979; azimran@gmail.com

(The authors would like to acknowledge fellow investigators Drs. Rene Heitner and Paul Fernhoff who have passed away.)

Introduction: Taliglucerase alfa is an enzyme replacement therapy (ERT) approved for treatment of adults with Type 1 Gaucher disease (GD) and is the first approved plant cell–expressed recombinant therapeutic protein. Safety and efficacy were evaluated in treatment-naïve adult patients in study PB-06-001 and the extension study PB-06-003.

Aim: To report long-term safety and efficacy results of 26 treatment-naïve adult patients with GD from study PB-06-001 who continued double-blind treatment in study PB-06-003.

Methods: Patients were randomized in PB-06-001 to receive taliglucerase alfa 30 or 60 U/kg every other week. Spleen volume, liver volume, hemoglobin concentration levels, platelet counts, and chitotriosidase activity were assessed through 36 months.

Results: At 36 months of treatment, the following changes were observed for taliglucerase alfa 30 and 60 U/kg, respectively: mean spleen volumes expressed in MN were reduced by 50.0% and 64.6%; mean liver volumes expressed in MN were reduced by 25.1% and 24.4%; mean hemoglobin concentrations increased by 1.8 and 3.0 g/dL; mean platelet counts increased by 29,783/mm^3 and 71,700/mm^3; and mean chitotriosidase activity decreased by 73.5% and 83.0%. All treatment-related adverse events (AEs) were mild/moderate and transient. The most common AEs were nasopharyngitis, arthralgia, upper respiratory tract infection, headache, and pain in extremity.

Discussion: These 36-month results of taliglucerase alfa in treatment-naïve adult patients with GD extend the taliglucerase alfa clinical safety and efficacy dataset.

Disclosure

This study was sponsored by Protalix Biotherapeutics. Editorial and medical writing support was provided by Peloton Advantage, LLC, and was funded by Pfizer. Pfizer and Protalix entered into an agreement in November 2009 to develop and commercialize taliglucerase alfa.

O-23

ENGAGE: A PHASE 3, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTI-CENTER STUDY TO INVESTIGATE THE EFFICACY AND SAFETY OF ELIGLUSTAT IN ADULTS WITH GAUCHER DISEASE TYPE 1: 18-MONTH RESULTS

Baris, H.[1†], Mistry, P.K. [2], Lukina, E.[3], Ben Turkia, H.[4], Ghosn, M.[5], Mehta, A.[6], Petakov, M.[7], Danda, S.[8], Hadjiev, E.[9], Angell, J.[10], Ross, L.[10], Peterschmitt, M.J. [10]

[1]Rabin Medical Center, Petach Tikvah, Israel; [2]Yale University School of Medicine, New Haven, Connecticut, USA; [3]Hematology Research Center, Moscow, Russia; [4]Hôpital La Rabta, Tunis, Tunisia; [5]Hôtel-Dieu de France University Hospital, Beirut, Lebanon; [6]The Royal Free Hospital, London, UK; [7]Clinical Center of Serbia, Belgrade, Serbia; [8]Christian Medical College, Vellore, Tamil Nadu, India; [9]University Hospital Alexandrovska, Sofia, Bulgaria; [10]Genzyme, a Sanofi company, Cambridge, MA, USA

†Presenting author: Hagit Baris Feldman, M.D.; Director of the Genetic Institute; Rambam Health Care Campus, Haifa, Israel; Phone: 972-4-8542456; Fax: 972-4-8543029; hb_feldman@rambam.health.gov.il

Introduction: Eliglustat, a ceramide analogue, is a novel oral substrate-reduction the development for Gaucher disease type 1 (GD1). We present 18-month results from ENGAGE (NCT00891202), a randomized, double-blind, placebo-controlled, Phase-3 trial (sponsored by Genzyme, a Sanofi company) investigating the efficacy and safety of eliglustat in untreated adults with GD1.

Methods: Forty patients (mean age: 31.8 years; 20 males) with splenomegaly and thrombocytopenia and/or anemia were randomized 1:1 to receive eliglustat (50 or 100 mg BID depending on plasma levels) or placebo for 9 month and then entered a 9-month open-label extension phase in which all patients received eliglustat. The primary efficacy endpoint was percent change in spleen volume (multiples of normal). Other efficacy measures included hemoglobin, liver volume, and platelets.

Results: In the 9-month primary analysis period, eliglustat was superior to placebo in all primary and secondary endpoints; no patients discontinued due to an adverse event. For 18/20 patients who have now received 18 months of eliglustat, mean improvements from baseline continue (spleen: -45%, hemoglobin: +1.02 g/dL; liver: -11%; platelets: +58%). For 20/20 patients previously receiving placebo, mean improvements after 9 months of eliglustat were consistent with what was seen in the primary analysis period in the eliglustat-treated patients: spleen: - 31%; hemoglobin: +0.79 g/dL; liver: -7.3%; platelets: +40%. No new safety concerns were identified.

Conclusion: ENGAGE met its primary and secondary efficacy endpoints. Patients from both treatment arms showed continued improvements in the first 9 months of the extension phase.

O-24

ENCORE: A RANDOMIZED, CONTROLLED, OPEN-LABEL NON-INFERIORITY STUDY COMPARING ELIGLUSTAT TO IMIGLUCERASE IN GAUCHER DISEASE TYPE 1 PATIENTS STABILIZED ON ENZYME REPLACEMENT THERAPY: 24-MONTH RESULTS

Peterschmitt, M.J.[1†], Cox, T.M. [2], Drelichman, G.[3], Cravo, R.[4], Balwani, M.[5], Burrow, T.A.[6], Martins, A.M.[7], Lukina, E.[8], Rosenbloom, B.[9], Ross, L.[1], Angell, J.[1], Puga, A.C.[1]

[1]Genzyme, a Sanofi company, Cambridge, MA, USA; [2]University of Cambridge, Addenbrooke's Hospital, Cambridge, UK; [3]Hospital de Niños Ricardo Gutiérrez, Buenos Aires, Argentina; [4]HEMORIO, Rio de Janeiro, RJ, Brasil; [5]Mount Sinai Hospital, New York, NY, USA; [6]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA; [7]Universidade Federal de São Paulo, São Paulo, SP, Brasil; [8]Hematology Research Center, Moscow, Russia; [9]Cedars-Sinai/Tower Hematology Oncology, Beverly Hills, CA, USA

†Presenter: M. Judith Peterschmitt, MD, Medical Director, Clinical Research; Genzyme, a Sanofi company, Phone: (617) 768-6663; Fax: (617) 768-9888; Judith.Peterschmitt@genzyme.com

Introduction: Eliglustat is a novel oral substrate-reduction therapy in development for adults with Gaucher disease type 1. This open-label Phase-3 trial (ENCORE, NCT00943111, Genzyme, a Sanofi company) evaluated eliglustat and imiglucerase in patients who had reached pre-specified therapeutic goals after ≥3 years of enzyme replacement therapy. We report efficacy data from the 12-month primary analysis period (PAP) and the first 12 months of the extension period in which all patients received eliglustat.

Methods: Patients were randomized 2:1 eliglustat: imiglucerase. The primary efficacy endpoint was percent of patients remaining stable on a composite of spleen, liver, hemoglobin, and platelet parameters. As this was a non-inferiority trial, efficacy analyses were performed on the per-protocol population (99 eliglustat, 47 imiglucerase patients).

Results: Eliglustat was non-inferior to imiglucerase: after 12 months, 85% of eliglustat and 94% of imiglucerase patients maintained all four goals (lower bound of 95% CI of difference [-17.6%] within the pre-specified [-25%] non-inferiority margin). 145 (91%) of the 159 patients treated in this study completed 24 months of treatment. Preliminary 12-month extension data demonstrates continued stability in spleen volume, liver volume, platelet count and hemoglobin level in most of the 99/106 patients who continued on eliglustat and the 46/53 patients who received imiglucerase in the PAP and then eliglustat in the trial extension. Most adverse events were mild or moderate in severity. No new safety concerns have arisen after 24 months.

Conclusions: In the Phase 3 ENCORE study, most patients maintained clinical stability while on eliglustat for 12 or 24 months.

O-25

COST-EFFECTIVENESS STUDIES IN GAUCHER AND FABRY DISEASE

Hollak, C.[1†], Biegstraaten, M.[1], van Dussen, L.[1], Rombach, S.[1], Dijkgraaf, M.[2]

[1]Department of Internal Medicine, division of Endocrinology and Metabolism, [2]Clinical Research Unit, Academic Medical Center, Amsterdam

†Presenting author: Carla E.M. Hollak; Department of Internal Medicine / Endocrinology and Metabolism; Academic Medical Center; Meibergdreef 9, 1105 AZ Amsterdam, the Netherlands; tel 020-5666967 ; fax 020 – 6919743 ; c.e.hollak@amc.nl

The Netherlands requested cost-effectiveness studies in relation to conditional reimbursement of enzyme replacement therapies (ERT) for Fabry disease. This treatment has a mean costs of € 200.000 per patient per year, which is comparable to costs for ERT in Gaucher disease. Because of limited effectiveness of ERT in the entire group of Fabry disease patients, the costs per quality adjusted life year (QALY) were extremely high, being around €3.3 million, discounted. For Gaucher disease, such analysis shows that the costs per QALY decrease substantially, when the treatment is more effective: using a life-time state-transition model (Markov model) ERT increases the years free of end organ damage by almost 13 years while the number QALY's increases by 6.3, resulting in costs per QALY of around € 325.000, discounted. Although this is still extremely high and beyond most national thresholds for cost-effectiveness, we suggest that the high effectiveness has contributed importantly to acceptance of reimbursement of ERT for GD I. We argue that these studies are needed to uncover limited effectiveness of some currently available orphan drug treatments. Discussions on acceptable returns of investments for orphan drugs and acceptable limits of costs for treatment of ultra rare diseases are needed. Collaborative efforts between EU member states, EMA, healthcare professionals, patients and industry should result in faster and improved cost-effectiveness analysis of orphan medicinal products, with the ultimate goal to offer equal access and effective treatment to patients.

O-26

NOVEL TREATMENT FOR GAUCHER DISEASE – ORAL ADMINISTRATION OF PLANT CELLS EXPRESSING GCD: PHASE 1 STUDY RESULTS AND PHASE 2a PROGRAM

Zimran, A.[1†], Rosenbaum, H.[2], Golembo, M.[3], Velitski, S.[3], Kivity, V.[3], Chertkoff, R.[3], Almon, E.[3], Shaaltiel, Y.[3]

[1]Gaucher Clinic, Shaare Zedek Medical Center, Jerusalem, Israel,
[2]Hematology Department, Rambam Health Care Campus, Haifa, Israel
[3]Protalix Biotherapeutics, Carmiel, Israel;
†Presenting author: Ari Zimran - azimran@hotmail.com

Enzyme replacement therapy with GCD has been successfully used for treatment of GD for more than twenty years. Although all three approved enzymes are safe and efficient, intravenous administration every two weeks remains a burden, affecting patients' quality of life. Therefore, oral Enzyme therapy has the advantage of the well-established therapeutic mechanism while providing continuous release rather than a bi-weekly bolus.

Taliglucerase alfa, an FDA approved ERT is expressed in carrot cells which may serve as natural capsules to protect human recombinant GCD from gastric degradation, due to the plant cell wall. This well-suited oral delivery method provides "ready to use" enzyme which requires no modifications to obtain optimal glycosylation for uptake to target cells.

In an open-label study, oral administration of carrot cells expressing GCD was found to be safe and well tolerated in all 16 Gaucher patients. Pharmacokinetic analysis following oral administration revealed continuous active GCD presence in patients' blood circulation for over ~30hrs. C_{max} analysis showed an average increase of over 100% in enzymatic activity from baseline, ranging from ~50% to ~350% among different patients. Thus, daily administration of Oral GCD is expected to achieve a steady state level of active enzyme in the patients' circulation. Meaningful, unexpected improvement in platelet counts was observed in 3/8 thrombocytopenic Gaucher patients after short-term treatment with Oral GCD. Data demonstrates platelet count increases ranging from 27% to 78% from base line.

A Phase 2A, 28 days, dose escalation study, designed to further determine the safety and pharmacokinetics of Oral GCD in Naïve Gaucher patients, will be described.

O-27

IDENTIFICATION OF microRNAs THAT MODULATE GLUCOCEREBROSIDASE ACTIVITY IN GAUCHER DISEASE CELLS

Siebert, M.[1,2], Westbroek, W.[1], Chen, Y-C.[3], Moaven, N.[1], Li, Y.[4], Velayati, A.[1], Saraiva-Pereira, M.L.[2,5,6], Martin, S.[3] and Sidransky, E.[1]

[1]Section on Molecular Neurogenetics, Medical Genetics Branch, National Human Genome Research Institute, National Institutes of Health, Bethesda, MD, 20892-3708, USA;
[2]Postgraduate Program in Cellular and Molecular Biology, Universidade Federal do Rio Grande do Sul, Porto Alegre, RS, 91501-970, Brazil;
[3]RNAi Screening Facility, National Center for Advancing Translational Sciences, National Institutes of Health, Rockville, MD, 20852, USA;
[4]Protein/Peptide Sequencing Facility, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD, 20892-3708, USA;
[5]Laboratory of Genetic Identification and Medical Genetics Service, Hospital de Clínicas de Porto Alegre, Porto Alegre, RS, 90035-903, Brazil;
[6]Department of Biochemistry, Universidade Federal do Rio Grande do Sul, Porto Alegre, RS, 90035-003, Brazil.

Gaucher disease (GD) is an autosomal recessive disorder caused by deficiency of the enzyme glucocerebrosidase (GCase). Although it is a monogenic disease, the phenotype in GD cannot always be predicted by the genotype. MicroRNAs (miRNAs) are a family of small non-coding RNAs involved in many biological processes and diseases. To determine whether miRNAs affect GCase activity and/or expression, we performed a high-throughput miRNA mimic screen consisting of 875 different miRNAs. The screen was done in Gaucher patient fibroblasts, and GCase activity was used as the initial outcome parameter. We found several miRNAs that up-regulated or down-regulated GCase activity. In follow-up assays, we confirmed that one specific miRNA down-regulated both GCase activity and protein levels by down-regulation of LIMP-2, the receptor for proper trafficking of GCase from the endoplasmic reticulum to the lysosome. A conditioned media assay confirmed that cells treated with this miRNA secreted GCase into the extracellular environment. Two other miRNAs, found to up-regulate GCase activity by greater than 40%, were confirmed to enhance GCase expression and protein levels as well. In conclusion, we show that miRNAs alter GCase activity in patient cells and may serve to modify disease manifestations in patients sharing the same genotype. Our data suggest that miRNAs may be acting as modifiers in Gaucher disease and may have utility as a novel therapeutic approach to up-regulate levels of GCase.

O-28

GAUCHER DISEASE AND PARKINSONISM: LONGITUDINAL CLINICAL CHARACTERIZATION AND PROGNOSIS

Lopez, G.[1†], Kim, J.[1], Groden, C.[2], Wiggs, E.[3], Tayebi, N.[1], Gonzalez, A.[1], Sidransky, E.[1]

[1]National Human Genome Research Institute (NHGRI), Medical Genetics Branch, Section of Neurogenetics, National Institutes of Health (NIH), Bethesda MD, USA
[2]NHGRI, Undiagnosed Disease Program, NIH, Bethesda MD, USA
[3]National Institutes of Neurological Disorders and Stroke, NIH, Bethesda MD, USA
†Corresponding author: Ellen Sidransky, M.D.; sidranse@mail.nih.gov

Objective: Longitudinal evaluation of patients with Gaucher disease and Parkinson disease in the Genetics Clinic at NHGRI for phenotypic characterization and prognosis.

Background: Mutations in the glucocerebrosidase (*GBA*) gene are the most common genetic risk factor associated with parkinsonism. The clinical presentation can be indistinguishable from classic Parkinson disease (PD) or patients can have features of atypical parkinsonian syndromes such as Dementia with Lewy bodies.

Methods: Individuals with both GD and PD were followed at NHGRI Genetic Clinic. Parameters including age of onset of GD symptoms, initial symptoms, use of enzyme replacement or substrate reduction therapy, genotype, severity, age of onset of PD symptoms, use of anti-parkinsonian medications, severity, disease duration, UPSIT score, age at death, and neurocognitive profile were analyzed.

Results: Patients with GD and PD have an earlier onset of PD symptoms. PD disease duration did not differ significantly from sporadic PD patients. Neurocognitive dysfunction was frequent, consistent with findings in the literature. There was no correlation between PD severity and *GBA* genotype, type or duration of Gaucher therapy and GD symptoms.

Conclusions: Disease duration in patients with GD and PD is similar to that seen in patients with sporadic PD. Extent and severity of PD symptoms varied significantly the mean age at death was younger, as expected with an earlier disease onset. Cognitive dysfunction including lack of concentration, short-term memory problems, and slow processing speed were frequently confirmed. Continued longitudinal follow-up of cohorts with GD and PD is essential for establishing the efficacy of any therapeutic interventions.

O-29

COMPARISON OF PARKINSON RISK IN ASHKENAZI JEWISH PATIENTS WITH GAUCHER DISEASE AND *GBA* HETEROZYGOTES

Dinur, T., Quinn, T., Sakanaka, K., Levy, O., Waters, C., Fahn, S., Dorovski, T., Chung, W.K., Pauciulo, M., Nichols, W., Rana, H.Q., Balwani, M., Bier, L., Elstein, D., Zimran, A., Alcalay, R.N.

IMPORTANCE Information on age-specific risk for Parkinson disease (PD) in patients with Gaucher disease (GD) and glucocerebrosidase (*GBA*) heterozygotes is important for understanding the pathophysiology of the genetic association and for counseling these populations.

OBJECTIVE

To estimate the age-specific risk for PD in Ashkenazi Jewish patients with type 1 GD and in *GBA* heterozygotes.

DESIGN, SETTING, AND PARTICIPANTS

The study included patients with GD from 2 tertiary centers, Shaare Zedek Medical Center, Jerusalem, Israel (n = 332) and Mount Sinai School of Medicine, New York, New York (n = 95). *GBA* noncarrier non-PD spouse control participants were recruited at the Center for Parkinson's Disease at Columbia University, New York (n = 77). All participants were Ashekanzi Jewish and most patients (98.1%) with GD carried at least 1 N370S mutation.

MAIN OUTCOMES AND MEASURES

The main outcome measure was a diagnosis of PD.

Diagnosis was established in patients with GD on examination. We used a validated family history interview that identifies PD with a sensitivity of 95.5%and specificity of 96.2% to identify PD in family members. Kaplan-Meier survival curves were used to estimate age-specific PD risk among patients with GD (n = 427), among their parents who are obligate *GBA* mutation carriers (heterozygotes, n = 694), and among noncarriers (parents of non-PD, non-GD control participants, n = 154). The age-specific risk was compared among groups using the log-rank test.

RESULTS

Among those who developed PD, patients with GD had a younger age at onset than *GBA* heterozygotes (mean, 54.2 vs 65.2 years, respectively; *P* = .003). Estimated age-specific risk for PD at 60 and 80 years of age was 4.7%and 9.1% among patients with GD, 1.5% and 7.7% among heterozygotes, and 0.7% and 2.1% among noncarriers, respectively. The risk for PD was higher in patients with GD than noncarriers (*P* = .008, log-rank test) and in heterozygotes than noncarriers (*P* = .03, log-rank test), but it did not reach statistical significance between patients with GD and *GBA* heterozygotes (*P* = .07, log-rank test).

CONCLUSIONS AND RELEVANCE

Patients with GD and *GBA* heterozygotes have an increased age-specific risk for PD compared with control individuals, with a similar magnitude of PD risk by 80 years of age; however, the number of mutant allelesmay play an important role in age at PD onset.

JAMA Neurol. doi:10.1001/jamaneurol.2014.313
Published online April 21, 2014

O-30

DISRUPTION OF MONOAMINE METABOLISM IN LYSOSOMAL STORAGE DISORDERS; A MECHANISTIC LINK TO PARKINSON'S DISEASE?

Heales, S., Burke, D., Neergheen, V. and Pope, S.

Department of Chemical Pathology, Great Ormond Street Hospital, Neurometabolic Unit, National Hospital & UCL Institute of Child Health, London, UK Simon.heales@gosh.nhs.uk

Background

The association between mutations affecting glucocerebrosidase (GBA1) and the risk of developing Parkinson's disease (PD) is well documented. However, development of PD may not just be associated with Gaucher disease but also other Lysosomal storage disorders (LSDs) [1]. Currently, the mechanism responsible for the loss of dopaminergic neurons and compromised lysosomal function is not known.

Methods

We measured cerebrospinal fluid (CSF) concentrations of the dopamine and serotonin metabolites, homovanillic acid (HVA) and 5-hydroxyindole acetic acid (5-HIAA), in patients with Gaucher disease, metachromatic leukodystrophy (MLD) and sanfillipo disease (MPS type III). Additionally, we documented the CSF concentration of pyridoxal phosphate (PLP) an essential cofactor for dopamine and serotonin synthesis.

Results

Evaluation of CSF revealed undetectable levels of HVA and 5-HIAA in a 66 year old male patient with Gaucher/Parkinson's. Impaired dopamine and serotonin turnover was also identified in a 37 year old female patient with enzymology suggestive of MLD. With regards to MPS III, we noted in 2 patients, decreased concentrations of PLP.

Conclusion

Our findings may indicate a vulnerability of monoamine neurotransmitter metabolism in some LSDs. Focus on dopamine and serotonin pathways is perhaps now required in order to help unravel the mechanistic link between LSDs and PD.

[1]. Shachar T, Lo Bianco C, Recchia A, Wiessner C, Raas-Rothschild A, Futerman AH.
Lysosomal storage disorders and Parkinson's disease: Gaucher disease and beyond. *Mov Disord.* 2011, 26 (9):1593-604.

O-31

THE CONNECTION BETWEEN ERAD, UPR, GAUCHER DISEASE AND PARKINSON'S DISEASE

Horowitz, M., Braunstein, H., Enoch, M. and Maor, G.
Department of Cell Research and Immunology, Tel Aviv University, 69978, Israel

Gaucher disease (GD) patients and carriers of GD mutations have a significantly higher propensity to develop Parkinson disease (PD) in comparison to the non-GD population.
Development of PD in carriers of GD mutations implies that the presence of a mutant GBA allele is a dominant predisposing factor. Dominance results either from haploinsufficiency or from gain of function. If haploinsufficiency accounts for the development of PD in carriers of GD mutations, it implies insufficient GCase activity in dopaminergic neurons. This should have happened also in macrophages, which should have accumulated glucosylceramide. However, accumulation of glucosylceramide has never been documented in cells that derive from carriers of GD mutations nor in brains of Type 1 GD patients, who are prone to develop PD. Alternatively, if dominance results from gain of function, then its development depends on the presence of deleterious product (mutant GCase).
We decided to study whether presence of mutant GCase leads to development of PD. To this end, we tested whether ER retention of mutant GCase upregulates the Unfolded Protein Response (UPR) in Gaucher disease derived cells and in cells carrying different GD mutations. We then developed fly models for carriers of GD mutations and tested development of Parkinson-like disease.
Our results show that continuous presence of mutant GCase, which undergoes ERAD, provokes the UPR machinery. We could recapitulate the development of parkinsonian signs in a *Drosophila* model heterozygous for the two fly endogenous alleles or in a fly expressing human mutant GCase variants in its serotonergic/dopaminergic cells.
Our results imply that ER retention of mutant GCase leads to ER stress, ERAD and UPR, and that this cellular stress leads to death of dopaminergic cells and development of PD.

O-32

VISUALIZATION OF ACTIVE GLUCOCEREBROSIDASES IN RODENT BRAIN WITH HIGH SPATIAL RESOLUTION BY FLUORESCENT ACTIVITY BASED PROBES

Herrera Moro Chao, D.[1,2], Kallemeijn, W.W.[1], Orre, M.[3], Ottenhoff, R.[1], Van Roomen, C.[1], Foppen, E.[2], Renner, M.[3], Marques, A.[1], Moeton, M.[3], Siljee, J.[2], Van Eijk, M.[1], Boot, R.[1], Kalsbeek, A.[2] and Aerts, J.M.F.G.[1]

[1]Department of Medical Biochemistry, Academic Medical Center, Amsterdam, The Netherlands, [2]Department of Endocrinology and Metabolism, Academic Medical Center, Amsterdam, The Netherlands and [3]Netherlands Institute for Neuroscience, Amsterdam, The Netherlands

Gaucher disease (GD) is characterized by lysosomal accumulation of glucosylceramide resulting from deficient activity of glucocerebrosidase (GBA). Glucosylceramide is also degraded in the cytosol of cells by the enzyme glucosylceramidase 2 (GBA2). The interest in GBA and glucosylceramide metabolism in the brain has recently been boosted by the finding that mutations in the GBA gene impose a risk factor for motor disorders such as ataxias and alpha-synucleinopathies. We earlier developed two classes of fluorescent activity based probes (ABPs) allowing *in vivo* and *in vitro* visualization of active molecules of GBA and GBA2 with high spatial resolution through covalent linkage to the catalytic nucleophile residues in their enzyme pockets. Here, we describe a method to visualize active GBA and GBA2 molecules in rodent brain by sequential intracerebroventricular administration of the ABPs. Brain areas related to motor control, like the basal ganglia and motor related structures in the brainstem, show the highest content on active GBA. Brain areas related to motivation and learning processes, as the hippocampus and limbic system, show significantly lower levels. The distribution of GBA2 markedly differs, being highest in the cerebellar cortex. The histological findings with ABP labeling were confirmed by biochemical analysis of isolated brain areas. Isolated astrocytes and microglia were found to express relatively little GBA2 as compared to neuronal cells, in particular Purkinje cells showing high levels.
In conclusion, ABP's offer sensitive tools to visualize both active GBA and GBA2 molecules in the brain and thus may find application to establish the role of these enzymes in neurodegenerative disease conditions such as alpha-synucleinopathies.

O-33

THE EFFECT OF PROTEASE INHIBITION ON LYSOSOMAL GLUCOCEREBROSIDASE

Oussoren, S.V., Scheij, S., Ferraz, M.J., Boot, R.G., Aerts, J.M.F.G.

Dept. Medical Biochemistry, Academical Medical Centre, Amsterdam

Breakdown of complex glycosphingolipids and glucosylceramide (GlcCer) is carried out stepwise and mainly occurs in endosomes and lysosomes. GlcCer is broken down into ceramide and glucose by the enzyme beta glucocerebrosidase. Three types of beta glucocerebrosidases exist: glucocerebrosidase 1 (GBA1), which is located within lysosomes, β-glucosidase 2 (GBA2) that is located in the plasma- and/or ER membrane and a cytosolic enzyme (GBA3). Patients with the lysosomal storage disorder Gaucher disease have only little GBA1 activity and therefore break down little to minute amounts of GlcCer, which causes build-up of GlcCer in lysosomes, especially in macrophages. Cathepsins form a class of proteases that exists of aspartyl (cathepsin D, E), serine (cathepsin A, G) and cysteine proteases (B, C, F, H, K/O, L1, L2/V, S, W, Z/X). Gene expression, protein levels and activity of several cathepsins have previously been found to be increased in Gaucher plasma, spleen and brain tissue. Cathepsins are involved in normal cellular functioning and protein turnover, as well as in apoptosis and necrosis. Furthermore, it is not known in what degree cathepsins act on GBA1 in lysosomes of cells in Gaucher disease. Theoretically, if it is discovered which of the cathepsins is primarily responsible for lysosomal breakdown of GBA1, inhibition of this cathepsin may prolong the half-life of the GBA enzyme within lysosomes. Using a fluorescent activity based probe for GBA1 (1), the various glycosylated forms of GBA1 can be visualised on SDS-PAGE gel. Upon cathepsin inhibition mostly the least glycosylated form of the enzyme is stabilized, since breakdown of the glycan chain can still occur.

(1) Novel Activity-Based Probes for Broad-Spectrum Profiling of Retaining b-Exoglucosidases In Situ and In Vivo. *Wouter W. Kallemeijn, Kah-Yee Li, Martin D. Witte, André R. A. Marques, Jan Aten, Saskia Scheij, et. Al.,* Angew. Chem. Int. Ed. 2012, 51, 12529 –12533

O-34

BONE ASSESSMENT IN SPANISH TYPE 1 GAUCHER DISEASE PATIENTS. THE ZAGAL PROJECT

Andrade, M.[1,2,3,4†] ,Alfonso, P.[2,3], Irun, P.[2,3,5] ,Garcia-Frade, J.[6], Lorenzo, J.F.[7], Luño, E.[8], Martin,.E.[9], Puerta, J.[10], de la Serna, J.[11], Villalon, L.[12], Pocovi, M.[2,3,5,12] , Roca, M.[12,13], Giraldo, P.[1,2,3,12]

[1]Haematology Department, Miguel Servet University Hospital, Zaragoza; [2]CIBER de Enfermedades Raras (CIBERER); [3]Aragon Institute of Health Sciences (IACS), Zaragoza, Spain. [4]Rio Hortega Researcher; [5]Biochemistry and Molecular and Cellular Biology Department, Zaragoza University, Zaragoza; [6]Haematology Department, Rio Hortega Hospital, Valladolid; [7]Internal Medicine Department, Burgos University Hospital; [8]Haematology Department, Central de Asturias University Hospital. Oviedo, [9]Haematology Department, Virgen de la Concha Hospital, Zamora; [10]Haematology Department, Virgen de las Nieves University Hospital, Granada, [11]Haematology Department, Alcorcon Fundation Hospital. Madrid; [12]Spanish Foundation for the Study and Therapy of Gaucher Disease (FEETEG) [13]International Skeletal Society-Radiodiagnostic Center

†Presenting author: Marcio Andrade-Campos; Traslational Research Unit, Miguel Servet University Hospital; Paseo Isabel La Catolica 1-3. Zaragoza, Spain 50009; mandrade@salud.aragon.es

Bone disease is the most serious manifestation of type 1 Gaucher disease (GD1); DEXA is the standard technique for BMD evaluation; the use of ultrasound instead X-rays to measure the amount of mechanical energy transmitted by the bone, and their speed of transmission reflecting the weakening bone structure.

Aim: To evaluate BMD in GD1 patients using an ultrasound technique (UD) in heel, and to study the effect of SRT on BMD.

From 63 adult GD1 included in ZAGAL study, between 2004-2013, 35 of them were evaluated by the same radiologist in the Unit of Expertise for LSD/FEETEG following the protocol of S-MRI, and DEXA/UD at baseline and every year. Genotype, clinical characteristics, surrogate biomarkers and response to therapy were evaluated. We are presenting the analysis of bone assessment after 2 and 5 years of continuing therapy with miglustat.

The majority of patients reported improvement of chronic bone pain, the mean (range) S-MRI scores at baseline and after 2 years on miglustat therapy were 9.6 points (0–25) and 7.2 points (0-21), respectively. Bone UD: among a total of 24 patients (naïve: 7; previous ERT: 17) indicated a statistically significant increase in BMD after 2 years on miglustat. The 5 years assessment showed a continuous improvement in BMD. One patient developed a bone crisis after 30 months on therapy without loss of BMD.

Conclusion: In our experience bone-UD is an useful tool to evaluate BMD in GD patients, combined with MRI provide an innocuous approach to follow-up bone response to therapy.

O-35

CHANGES IN PERIPHERAL BLOOD OSTEOCLAST CULTURES IN RELATION TO FEATURES OF BONE DISEASE IN ADULT GD1 PATIENTS.

Cunningham, N., Bauernfreund, Y., Reed, M., Mehta, A.B., Hughes, D.A.

Lysosomal Storage Disorders Unit; Royal Free London NHS Foundation Trust
London, NW3 2QG, rmgvdah@ucl.ac.uk

Introduction: Bone complications in Gaucher disease (GD) include bone pain, reduced bone density, lytic lesions, pathological fractures and avascular necrosis and occur along side of bone marrow infiltration. As with other features of GD presentation is heterogeneous and not predicted by genotype. Our previous studies have demonstrated an increased number of osteoclasts cultured from the peripheral blood of patients with GD compared with controls and a relationship on an individual patient level between osteoclast numbers and presentation of bone disease.

Objective: To systematically examine the relationship between bone complications, osteoclast numbers and other biological features in patients with GD attending a single centre in the UK

Patients and Methods: Osteoclasts cultured from peripheral blood were examined in 68 GD patients (38 male, 30 female, range 19-78 years) over 171 visits during 10 years follow up and compared with features of bone pathology including bone mineral density , BMB score on skeletal MRI, bone pain, joint replacement, episodes of avascular necrosis, overall severity score and bone dimension of the GD-DS3 score.

Results: Number of osteoclasts cultured/coverslip ranged from 3-446. Patients with stable disease cultured similar osteoclast numbers with each visit whereas patients with improvement in biological features exhibited reduction in osteoclast numbers. Direction of change of BMD, and bone dimension of the DS3 score correlated with changes in osteoclast numbers.

Conclusions: Measurement of PB osteoclasts may provide an instrument for monitoring bone health and response to therapy. Further analysis of its value in prediction of bone events is required.

O-36

PROINFLAMMATORY AND PROOSTEOCLASTOGENIC POTENTIAL OF PERIPHERAL BLOOD MONONUCLEAR CELLS FROM GAUCHER PATIENTS: IMPLICATION FOR BONE PATHOLOGY

Mucci, J.M.[1†], Cuello, M.F.[2], Kisinovsky, I.[3], Larroude, M.[4], Delpino, M.V.[5]; Rozenfeld, P.[1]

[1]IIFP, Departamento de Ciencias Biológicas, Facultad de Ciencias Exactas, Universidad Nacional de La Plata- CONICET. La Plata. [2]Servicio de Hematología,Hospital de Niños "Sor María Ludovica", La Plata. [3]Sanatorio Urquiza, Quilmes. [4] Consultorio Larrea Nº 1106 3ºE, Buenos Aires. [5] Instituto de Inmunología, Genética y Metabolismo (INIGEM). Hospital de Clínicas "José de San Martín", Facultad de Medicina, Universidad de Buenos Aires, Buenos Aires. Argentina.
†e-mail: paularozenfeld@gmail.com

The aim of our work was to evaluate the proinflammatory and proosteoclastogenic environment in circulation of patients with Gaucher disease. The study was performed using PBMC from patients under ERT. Percentage of two different monocyte subsets and the production of proinflammatory cytokines were evaluated by flow cytometry. To evaluate the proosteoclastogenic state PBMC from patients were cultured in the presence of M-CSF and RANKL and osteoclast differentiation and activity were assayed. These experiments were carried out in the presence of Velaglucerase to study the effect of ERT. To evaluate the presence of secreted molecules that induced osteoclast differentiation conditioned media (CM) prepared from patients PBMC was used in osteoclastogenesis induction assays and the involvement of TNF-α and RANKL was evaluated using neutralizing molecules. Percentage of the proinflammatory $CD14^{+}CD16^{+}$ monocyte subset was significantly higher on patients ($p<0,001$) and an increased production of proinflammatory cytokines was observed for T cells and monocytes in patients. Osteoclastogenesis was higher in patients ($p<0,01$) and *in vitro* Velaglucerase treatment reduced osteoclast levels and activity to control levels. The induction of osteoclast differentiation by CM was higher by patient's CM compared to healthy controls ($p<0,001$) and this effect partially involved TNF-α and RANKL. In conclusion we have shown a potential involvement of two monocyte subsets in the proinflammatory state present in patients with Gaucher disease. PBMC from patients show higher osteoclastogenesis which is reduced by in vitro Velaglucerase treatment. TNF-α and RANKL would be involved in the potential proosteoclastogenic state in patients.

This work was supported by a grant from Shire (USA) [IIR-ARG-000120 to PR].

O-37

CAN WE QUANTIFY HOW EFFECTIVE IS THE TREATMENT FOR GAUCHER DISEASE? LESSONS FROM A COCHRANE REVIEW

Shemesh, E.[1†], Deroma, L.[2], Bembi, B.[2], Deegan, P.[3], Hollak, C.[4], Weinreb, N.J. [5,6], Cox, T.M. [3]

[1]Department of Clinical Biochemistry, Ben-Gurion University of the Negev, Beer Sheva, Israel
[2]Regional Coordinator Centre for Rare Diseases, University Hospital "Santa Maria della Misericordia", Udine, Italy
[3]Department of Medicine, University of Cambridge and Lysosomal Disorders Unit, Cambridge, UK
[4]Department of Internal Medicine, Division of Endocrinology & Metabolism, Academic Medical Center, Amsterdam, Netherlands
[5]University Research Foundation for Lysosomal Storage Diseases, Northwest Oncology Hematology Associates PA, Coral Springs, Florida, USA
[6]University of Miami Miller School of Medicine, Miami, Florida, USA
†Elad234@gmail.com

The efficacy, safety, and doses of GD medications have not been systematically evaluated. We systematically reviewed all randomized clinical trials(RCTs) assessing GD treatments. Included were quasi/fully-randomized studies assessing enzyme replacement and/or substrate reduction therapies (ERT,SRT). Two authors independently assessed trial quality using Cochrane criteria. Mean difference of treatment effect was calculated.

Eight of 488 retrieved studies met inclusion criteria (n=300). Half evaluated pre-treated patients, 7 enrolled GD1 patients; 1 evaluated GD3. Two studies assessed SRT. Only 1 study scored 'low-risk of bias'. No severe adverse events were reported. Imiglucerase compared withalglucerase(60U/kg)(MD0.19, 95%CI-76 to 1.14) or compared to velaglucerase-alfa(60U/kg)(MD0.15, 95%CI-0.55 to 0.85), similarly altered haemoglobin at 9 months in treatment-naïve patients even when excluding splenectomized patients. Different doses of taliglucerase or velaglucerase-alfa similarly increased haemoglobin. Imiglucerase improved platelet counts in patients with intact spleens more than velaglucerase-alfa(60U/kg)(MD-79.87, 95%CI -137.57 to -22.17). Spleen and liver volumes decreased similarly with all ERT/doses. Although no differential dose effect on serum biomarkers was seen at 9 months, a significantly greater reduction was reported with higher velaglucerase dose at 1year. Two ERT maintenance trials comparing similar cumulative doses administered every 2 versus 4weeks revealed no significant differences in haemoglobin, platelets or organ volumes over 6-12 months.

Evidence–based medicine for rare diseases is beset by numerous obstacles, particularly when moving from ground-breaking discoveries to delicate therapy optimization. More flexible inclusion criteria, including non-randomized studies, may be warranted. This may require developing acceptable statistical tools to rate the "confidence level" of trials employing less-conventional experimental designs.

O-38

LIMITS ON USE OF HEALTH ECONOMIC ASSESSMENTS FOR RARE DISEASES

Hyry, H.I.[1], Stern, A.D.[2], Cox, T.M.[1], Roos, J.C.P.[1†]

1) Department of Medicine, University of Cambridge, Cambridge CB2 0QQ, UK and 2) Harvard University, Cambridge, MA 02138, USA

†Presenting author: Jonathan C P Roos (MA, MB, BChir, PhD (Cantab)), jcpr2@cam.ac.uk

BACKGROUND: Funding of expensive treatments for rare diseases is contentious. These agents fare poorly on 'efficiency' or health economic measures, such as the quality-adjusted life years, because of high cost and frequently poor gains in quality of life and survival.

METHODS: We test the soundness of cost-effectiveness methods using a novel economic and ethical analysis.

RESULTS: We show that cost-effectiveness assessments are limited in several important and often fundamental ways and inadequate as the sole basis for making decisions about treatment. However, if appropriately devised, cost-effectiveness assessments will have targeted use in the orphan disease context and beyond—in particular, in cases where comparative-effectiveness research can be applied to improve cost-efficiency without sacrificing the best chances of patients who are ill.

CONCLUSIONS: Those who suffer from treatable rare diseases have become a public symbol of perceived fiscal excess in modern medicine. But finger-pointing and flawed arguments should be resisted. Denying their funding based on cost and low efficacy or efficiency is only superficially attractive and a careful examination shows that health economic approaches are limited in several important ways.

For more details, please see our article published in QJM. 2014 Mar;107(3):241-5 (http://qjmed.oxfordjournals.org/content/107/3/241.long)

Disclosure/funding statements

The work has received no direct funding. In the last three years J.C.P.R., H.I.H. and T.M.C. have attended symposia and received hospitality from the UK Gaucher Association, the Susan Lewis Memorial Fund and the European Working Group on Gaucher disease and funding from the Helen Manuel Foundation towards publication costs. T.M.C. has received research support from the UK government, as well as unrestricted research grants from Genzyme and Shire, and he advises pharmaceutical companies engaged in the orphan disease setting, including Actelion, Genzyme, Shire, Amicus Therapeutics, and Protalix Biotherapeutics, receiving speakers' fees and travel costs. H.I.H. has had two younger sisters die of an orphan disease. There are no other relationships or activities that could appear to have influenced the submitted work. A.D.S. has no conflict of interest.

O-39

THE LEGAL IMPERATIVE FOR TREATING RARE DISORDERS

Hyry,H.I. [1†], Roos, J.C.P.[1], Manuel, J.[2], Cox, T.M.[1]

1) Department of Medicine, University of Cambridge, Cambridge CB2 0QQ, UK and 2) European Gaucher Alliance, UK Gauchers Association, 340 West End Lane, London NW6 1LN, UK

†Presenting author contact details : Hanna Hyry (MA Oxon, A Cantab) hannaihyry@gmail.com

BACKGROUND: Life-saving orphan drugs are some of the most expensive medicines. European Union governments aim to accommodate their provision within stretched healthcare budgets but face pressure to reduce funding of such treatments. Patients struggle to retain or gain access to them as their special status is questioned, causing distress and in some cases, fears of premature death. In the UK and EU reimbursement and pricing model of drugs, and orphan drugs in particular, is being re-evaluated.

METHODS: Using the United Kingdom as a case study we present, for the first time, legal arguments which compel governments to provide orphan medicinal products. These include (i) disability legislation, (ii) national and organisational constitutions, (iii) judicial review, (iv) tort law and (v) human rights legislation. We then address directly potential objections to our analysis and counter arguments which aim to limit provision of orphan drugs to the intended patient recipients.

RESULTS: We demonstrate that a compelling case can be made that the law demands the treatment of orphan diseases.

CONCLUSIONS: Our legal framework will assist doctors and patients in ensuring the continued provision of treatments despite significant economic pressure to reduce funding. These legal avenues will empower stakeholders in drafting funding guidelines throughout the EU. The legal right to treatment extends beyond rare diseases and our analysis may therefore affect allocation of healthcare budgets throughout the EU.

For more details, please see our article published in Orphanet J Rare Dis. 2013 Sep 6;8:135. doi: 10.1186/1750-1172-8-135 (http://www.ojrd.com/content/8/1/135)

Disclosure/funding statements

The work has received no direct funding. The following financial relationships with organisations might have an interest in the submitted work in the previous three years: HIH and JCPR have received funding from the European Gaucher Alliance and Susan Lewis Memorial Fund, and HIH from the Helen Manuel Foundation. JCPR has attended symposia and received hospitality from Shire Human Genetic Therapies and speaking fees from the Genzyme Corporation and Actelion Pharmaceuticals. JM has received travel grants to attend industry sponsored meetings from Genzyme, Shire, Protalix and Pfizer. The EGA of which JM is Chairman receives unrestricted grants to support its activities from Genzyme, Shire, Protalix, Pfizer, Amicus and Actelion. The UK Gauchers Association has received sponsorship from Genzyme, Shire and Protalix for its UK activities and following his retirement as Chairman of the UK Gauchers Association, Genzyme presented an unrestricted and unsolicited donation to the UK Gauchers Association in his honour to be used to support Gaucher related activities at his discretion with agreement of the Board of the UK Gauchers Association. TMC has receives research support from the UK government, as well as unrestricted research grants from Genzyme and Shire, and he advises pharmaceutical companies engaged in the orphan disease setting, including Actelion, Genzyme, Shire, Amicus Therapeutics, and Protalix Biotherapeutics, receiving speakers' fees and travel costs. HIH has had two younger sisters die of an orphan disease. There are no other relationships or activities that could appear to have influenced the submitted work.

POSTERS

P-01	**DUP 24PB IN CHIT1 IN SIX MEXICAN AMERINDIAN POPULATIONS** *Garcia-Ortiz, J.E., Juárez-Osuna, J.A., Porras-Dorantes, A., Juarez-Rendón, K.J., Magaña-Torres, M.T., Sandoval-Ramírez, L., Da Silva-Jose, T.D. - MEXICO*
P-02	**GAUCHER'S DISEASE: EVIDENCE OF FOUNDER EFFECT IN A POPULATION FROM TABULEIRO DO NORTE, NORTHEASTERN BRAZIL** *Chaves, R.G., Veiga Pereira, L., Tófoli, F., Rosemberg, R., Fernandes Carvalho, M.D., Carneiro Coelho, J., Michellin-Tirelli, K., de Freitas Chaves, M., Cavalcante Junior, G.B.- BRAZIL*
P-03	**GBA MUTATIONAL SPECTRUM OF NEWLY DIAGNOSED HUNGARIAN PATIENTS WITH GAUCHER DISEASE** *Juhász, P., Tóth, B., Csorba, G., Maródi, L., Erdős, M. - HUNGARY*
P-04	**CLINICAL CONTEXT OF THE PATIENT WITH GAUCHER DISEASE: NOTHING IS UNIFACTORIAL** *Paskulin, L., Koppe, T., Uribe Cruz, C., Doneda, D., Siebert, M., Maffazzioli Santos, L., Vairo, F., Schwartz, I.V.D. - BRAZIL*
P-05	**GENOTYPE/PHENOTYPE DISCREPANCY IN GAUCHER DISEASE TYPE 3: CASE REPORT** *Martins, A.M., Curiati, M.A.; Rand, M.; Mendes, C. - BRAZIL*
P-06	**EVALUATION OF SINGLE NUCLEOTIDE POLYMORPHISMS IN SCARB2, PSAP AND CLN8 GENES IN A GROUP OF BRAZILIAN PATIENTS WITH GAUCHER DISEASE** *Siebert, M., Vasata Furtado, G., Saraiva-Pereira, M.-L. - BRAZIL*
P-07	**IDENTIFICATION OF THE ACID/BASE AND NUCLEOPHILE IN ALL HUMAN RETAINING BETA-GLUCOSIDASES** *Kallemeijn, W.W., Witte, M.D., Voorn-Brouwer,T.M., Walvoort, M.T.C., Li, K-Y., Codée, J.D.C., van der Marel, G.A., Boot, R.G., Overkleeft, H.S. and Aerts, J.M.F.G. – the NETHERLANDS, USA*
P-08	**ACTION MYOCLONUS-RENUL FAILURE SYNDROME: DIAGNOSTIC APPLICATIONS OF ACTIVITY-BASED PROBES AND LIPID ANALYSIS** *Gaspar, P., Kallemeijn, W.W., Strijland, A., Scheij, S., Van Eijk, M., Aten, J., Overkleeft, H.S., Balreira, A., Zunke, F., Schwake, M., Miranda, C.S. and Aerts, J.M.F.G. – PORTUGAL,the NETHERLANDS, GERMANY*
P-09	**A MODIFIED METHOD FOR THE DETERMINATION OF ACID BETA-GLUCOSIDASE IN DRIED BLOOD SPOT SAMPLES AS A DIAGNOSTIC APPROACH IN THE ANDEAN COUNTRIES: PRELIMINARY RESULTS** *Pacheco, N. & Uribe, A. - COLOMBIA*
P-10	**MONOCYTE RESPIRATORY BURST CAPACITY AND LYMPHOCYTE SUBSETS IN GAUCHER TYPE 1 PATIENTS** *Rodic, P., Janic, D., Popadic, D., Suvajdzic Vukovic, N., Kraguljac Kurtovic, N., Djordjevic, M., Mitrovic, M. - SERBIA*
P-11	**ROLE OF RED BLOOD CELL ON THE PATHOPHYSIOLOGY OF GAUCHER DISEASE AND EFFECT OF THE ENZYME REPLACEMENT THERAPY** *Franco, M., Marin, M., Reihani, N., Collec, E., Billette de Villemeur, T., Rose, C., Mignot, C., Colin, Y., Belmatoug, N. & Le Van Kim, C. - FRANCE*
P-12	**GAUCHEROMAS: WHEN MACROPHAGES PROMOTE TUMOR FORMATION AND DISSEMINATION** *Goker-Alpan, O., Limgala, R.P., Ivanova, M., Hebert, A., Komlodi-Pasztor, E., Elstein, D., Rosenbaum, H., Zimran, A. - ISRAEL*
P-13	**FALSE NEGATIVE RESULT IN β–GLUCOSERBROSIDASE ASSAY OF A GAUCHER'S DISEASE PATIENT WITH PLASMA CELL LEUKEMIA** *Deutsher-Chertkow, Y., Zhilin-Roth, A., Chen Zion, Y., Sarig, G., Rosenbaum, H. - ISRAEL*
P-14	**PROINFLAMMATORY PROFILE BETWEEN MULTIPLE MYELOMA AND GAUCHER DISEASE** *Gervas-Arruga, J., Andrade, M., Giraldo, P. - SPAIN*

P-15	**CLINICAL COURSE OF TWO PATIENTS WITH GAUCHER DISEASE, MGUS AND MULTIPLE MYELOMA** *Donner, M.G., Santosa, D., Häussinger, D., vom Dahl, S. - GERMANY*
P-16	**BRAZILIAN PATIENTS WITH GAUCHER DISEASE PRESENT INCREASED SERUM β2-MICROGLOBULIN** *Koppe, T.B., Heineck, B.L., Paskulin, L.D., Camargo, M.B., Doneda, D., Donis, K.C., Vairo, F., Daudt, L.E., Schwartz, I.V. - BRAZIL*
P-17	**RELATIONS BETWEEN AUTOPHAGY, LYSOSOMAL PERMEABILIZATION AND LYSOSOMAL STORAGE** *Pupyshev, A.B. - RUSSIA*
P-18	**GLYCOPROTEIN NONMETASTATIC MELANOMA PROTEIN B IS A SENSITIVE MARKER FOR LYSOSOMAL LIPID OVERLOAD IN MACROPHAGES** *Lizama, Tanit., Marques, A., Tol, M., Ottenhof, R., van Roomen , C., Aten, J., Claessen, N., Argmann, C., Aerts, J.M.F.G., van Eijk, M. – the NETHERLANDS*
P-19	**THE PROGNOSTIC VALUE OF THE SERUM FERRITIN LEVELS IN GAUCHER DISEASE** *Koppe, T.B., Heineck, B.L., Paskulin, L.D., Camargo, M.B., Doneda, D., Donis, K.C., Vairo, F., Daudt, L.E., Schwartz, I.V. - BRAZIL*
P-20	**ORIGIN OF PLASMA GLYCOSPHINGOLIPIDS: INVOLVEMEMNT OF ABCA1** *Ghauharali-van der Vlugt, K., Kallemeijn, W., Scheij, S., Ottenhoff, R., P.A.A. van Roomen, C., Vergeer, M., Motazacker, M., Groen, A.K., Aerts, J.M. F.G., and Groener, J.E.M. – the NETHERLANDS*
P-21	**α-SYNUCLEIN DIMERIZATION IN ERYTHROCYTES OF GAUCHER DISEASE PATIENTS IN RELATION TO LIPID ABNORMALITIES AND OXIDATIVE STRESS** *Moraitou, M., Dermentzaki, G., Dimitriou, E., Monopolis, I., Dekker, N., Aerts, H., Stefanis, L. and Michelakakis, H. – GREECE, the NETHERLANDS*
P-22	**α-SYNUCLEIN RS356219 POLYMORPHISMS IN PATIENTS WITH GAUCHER DISEASE AND PARKINSON DISEASE** *Ioscovich, D., Altarescu, G., Alcalay, R.N., Zimran, A., Elstein, D. – ISRAEL, USA*
P-23	**GBA 1 AND 2, FACTORS TO CONSIDER IN PARKINSON'S DISEASE?** *Burke, D., Vellodi, A., and Heales, S. – UNITED KINGDOM*
P-24	**STUDY OF THE DISTRIBUTION OF DERIVATIVES OF L-IDONOJIRIMYCIN IN NERVOUS TISSUES** *Alfonso, P., Gervas, J., Andreu, V., García-Moreno, I., Mari-Beffa, M.M., Urdiales Ruiz, J.L., Sánchez-Jiménez, F., Ortiz-Mellet, C., García-Fernández, J.M., Giraldo, P. - SPAIN*
P-25	**BRAIN-DERIVED NEUROTROPHIC FACTOR INCREASES AFTER ENZYME REPLACEMENT THERAPY IN GAUCHER DISEASE** *Vairo, F., Sperb-Ludwig, F., Wilke, M., Michellin-Tirelli, K., Burin, M., Netto, C., Neto, E.C., Schwartz, I. - BRAZIL*
P-26	**CORRELATION BETWEEN BRAIN MR SPECTROSCOPY AND BMB SCORE IN TYPE 1 GAUCHER'S DISEASE: IS THERE ANY?** *Bertholdo, D., Vairo, F., Vanz, A.P., Vedolin, L., Schwartz, I. - BRAZIL*
P-27	**GAUCHER DISEASE TYPE 3A TREATMENT WITH TALIGLUCERASE** *Cravo, R., Jardim, E., Rotman, V., Guimarães de Noronha, T., de Sousa Maia, M.de L.- BRAZIL*
P-28	**FATIGUE SCORE GAUCHER DISEASE (FSGD): A NEW TOOL TO ASSESS FATIGUE IN TYPE I GAUCHER DISEASE** *Reinke, J., Krause, J., Mengel, E. - GERMANY*
P-29	**RETHINKING FATIGUE IN GAUCHER DISEASE** *Chen Zion, Y., Pappadopulos, E., Wajnrajch, M., Sandberg, D.E., Rosenbaum, H. – ISRAEL, USA*
P-30	**SKELETAL MANIFESTATIONS IN GAUCHER DISEASE, MORE THAN BONE CRISIS** *Andrade-Campos, M., Roca, M., Giraldo, P. - SPAIN*
P-31	**HEALTH-RELATED QUALITY OF LIFE OF IN PATIENTS WITH GAUCHER DISEASE AND HIP OSTEONECROSIS** *Mansano, L., Bregman, A., Elstein, D., Zimran, A., Lebel, E. - ISRAEL*

P-32	**LONGEVITY OF HIP ARTHROPLASTY IN PATIENTS WITH GAUCHER DISEASE** *Abu-Dalu, K., Elstein, D., Zimran, A., Peyser, A., Lebel, E. - ISRAEL*
P-33	**BMP and Wnt SIGNALING INFLUENCES ON BONE HOMEOSTASIS IN TYPE I GAUCHER DISEASE** *Zancan, I., Bellesso, S., Costa, R., Salvalaio, M., Filocamo, M. and Moro, E. - ITALY*
P-34	**ASSESSMENT OF BONE MARROW MICROVASCULAR NETWORK SUPPORTS THE CHRONIC INFLAMMATION CONCEPT IN UNTREATED GAUCHER DISEASE TYPE 1** *Klimkowska, M., Palmblad, J., Machaczka, M. - SWEDEN*
P-35	**DELINEATION OF BONE CRISES IN THE SMALL BONES OF THE HANDS AND FEET IN PATIENTS WITH TYPE 1 GAUCHER DISEASE** *Baris, H.N., Weisz Hubshman, M., Kornreich, L., Bar-Sever, Z. and Cohen, I.J. - ISRAEL*
P-36	**A CASE OF SUCCESSFUL SURGICAL TREATMENT OF BONE COMPLICATIONS IN SPLENECTOMIZED CHILD WITH GAUCHER DISEASE TYPE 1** *Gundobina, O., Movsisyan, G., Namazova-Baranova, L., Malahov, O. - RUSSIA*
P-37	**GAUCHER DISEASE AND BONE PROINFLAMMATORY PROFILE UNDER MIGLUSTAT THERAPY** *Gervas-Arruga, J., Andrade, M., Roca, M., Giraldo, P. - SPAIN*
P-38	**MONITORING BONE MARROW INVOLVEMENT IN GAUCHER DISEASE USING BONE MARROW BURDEN SCORE** *Bertholdo, D., Vairo, F., Camargo, M., Vanz, A.P., Vedolin, L., Schwartz, I. - BRAZIL*
P-39	**ASSESSMENT OF LIVER AND SPLEEN FIBROSIS IN PATIENTS WITH GAUCHER DISEASE USING FIBROSCAN** *Rosenbaum, H., Chen-Zion, Y., Nimer, A. - ISRAEL*
P-40	**NEGATIVE ROLE OF SPLENECTOMY IN GAUCHER DISEASE: RUSSIAN EXPERIENCE** *Lukina, K., Sysoev,a E., Yatsyk, G., Mamonov, V., Maksimov, A., Lukina, E. - RUSSIA*
P-41	**AN INTRIGUING CASE OF TYPE 1 GAUCHER DISEASE WITH UNCOMMON MANIFESTATIONS** *Cassinerio, E., Poggiali, E., Casirati, G., Nava, I., Duca, L., Baldini, I.M., Soverini, G., Cappellini, M.D. - ITALY*
P-42	**ANALYSIS OF INTESTINAL SACCHARIDASES PROFILE IN PATIENTS WITH GAUCHER DISEASE** *Medrano-Engay, B., Irun, M.P., Andreu, V., Alfonso, P., Bajador, E., Pocovi, M., Giraldo, P. - SPAIN*
P-43	**TEN YEARS OF EXPERIENCE WITH MIGLUSTAT IN TREATMENT OF TYPE 1 GAUCHER DISEASE: THE SPANISH ZAGAL PROJECT** *Giraldo, P., Andrade, M., Alfonso, P., Irun, P., Atutxa, K., Acedo, A., Barez, A., Blanes, M., Diaz-Morant, V., Fernandez-Galán, M.A., Franco, R., Gil-Cortes, C., Giner, V., Ibañez, A., Latre, P., Loyola, I., Luño, E., Martin, E., Puerta, J., Roig, I., de la Serna, J., Salamero, O., Villalon, L., Pocovi, M. - SPAIN*
P-44	**ASSESSMENT OF GHRELIN, LEPTIN, ADIPONECTIN AND INSULIN LEVELS IN GAUCHER DISEASE TYPE I PATIENTS IN ENZYME REPLACEMENT THERAPY** *Doneda, D., Lopes, A.L., Teixeira, B.C., Mittelstadt, S.D., Vairo, F., Schwartz, I.V.D. - BRAZIL*
P-45	**CLINICAL RESPONSE TO ELIGLUSTAT IN TREATMENT-NAÏVE PATIENTS WITH GAUCHER DISEASE TYPE 1 (GD1): POST-HOC COMPARISON TO IMIGLUCERASE IN A REAL-WORLD SETTING** *Mankoski, R., Taylor, J.S., Angell, J., Peterschmitt, M. J. - USA*
P-46	**ELECTROCARDIOGRAPHIC EVALUATION OF ELIGLUSTAT: RESULTS OF A THOROUGH QT STUDY AND PHASE 2 AND 3 STUDIES** *Peterschmitt, M. J., Ruskin, J.N., Ortemann-Renon, C., Ross, L., Mankoski, R., Puga, A. C., von Moltke, L., Cox, G.F. - USA*
P-47	**LONG TERM EFFICACY AND SAFETY OF VELAGLUCERASE IN SIX PATIENTS WITH TYPE 1 GAUCHER DISEASE PREVIOSLY TREATED WITH IMIGLUCERASE** *Ciana, G., Sechi, A., Dardis, A., Malini, E., Zanin, I., Romanello, M., Brondani, G., Cattarossi, S., Macor, D. and Bembi, B. - ITALY*

P-48	**SAFETY OF USE OF VELAGLUCERASE IN SIX PATIENTS WITH TYPE 1 GAUCHER DISEASE SHIFTED FROM IMIGLUCERASE** *Ciana, G., Sechi, A., Dardis, A., Malini, E., Zanin, I., Romanello, M., Brondani, G., Cattarossi, S., Macor, D. and Bembi, B. - ITALY*
P-49	**FOLLOW-UP OF ADULT PATIENTS WITH TYPE 1 GAUCHER DISEASE ON TALIGLUCERASE ALFA: A STUDY BASED ON BONE MAGNETIC RESONANCE** *Mittelstadt, S.D., Vairo, F., Bertholdo, D., Schwartz, I.V.D. - BRAZIL*
P-50	**INITIAL RESPONSE TO ERT FOLLOWED BY WHOLE BODY MRI** *Mengel,E., Moos,L., Reinke,J., Heidrich,A., Brixius-Huth, M., Staatz, G. - GERMANY*
P-51	**THE EUROPEAN GAUCHER ALLIANCE (EGA): A PROJECT TO TAKE FORWARD THE NEXT GENERATION OF LEADERS NATIONALLY AND INTERNATIONALLY** *Lauridsen, A.-G., Cook, J., Tomova, R., Parkkinen, J. – UNITED KINGDOM*
P-52	**THE EUROPEAN GAUCHER ALLIANCE (EGA): A SURVEY OF MEMBER PATIENT ORGANISATION'S ACTIVITIES, HEALTHCARE ENVIRONMENTS AND CONCERNS** *Žnidar, I., Collin-Histed, T., Niemeyer, P., Parkkinen, J., Lauridsen, A.-G., Zariņa, S., Cohen, Y., Manuel, J.- UNITED KINGDOM*

P-01

DUP 24PB IN *CHIT1* IN SIX MEXICAN AMERINDIAN POPULATIONS

Garcia-Ortiz, J.E.[†], Juárez-Osuna, J.A., Porras-Dorantes, A., Juarez-Rendón, K.J., Magaña-Torres, M.T., Sandoval-Ramírez, L., Da Silva-Jose, T.D.

Laboratorio de diagnóstico de enfermedades lisosomales. División de Genética, Centro de Investigación Biomédica de Occidente, CMNO-IMSS. Guadalajara, Jalisco, México.

[†]Corresponding author: Jose Elias Garcia-Ortiz; e-mail: jose.elias.garcia@gmail.com

Introduction: In chitotriosidase (*CHIT1*), a biomarker used in Gaucher disease, 24pb duplication is the most frequent polymorphism at *CHIT1* and results in deficient enzymatic activity compromising its use as biomarker. In this study we wanted to determine the allelic and genotypic frequency of dup 24pb on six Mexican Amerindian populations.

Material and methods: 692 samples were analized: Purepechas (49), Tarahumaras (97), Huicholes (97), Mayan (139), Tenek (97) and Nahuas (213). DNA extraction and PCR was done as published elsewhere. Statistical analysis was done by direct counting of genotype and allele frequencies and HWE were using a chi-square and Markov chain by Arlequin 3.5.

Results: We found the dup 24pb (*CHIT1*) in distributions observed in Table 1. All groups were in HWE. The allele frequency of dup 24pb was higher than expected in all analyzed groups compared with Mexican mestizo.

Table 1. dup 24 bp in Mexican Amerindian populations

Populations	Number	Genotype Frequencies (%)			Allele Frequencies (%)		Hardy-Weinberg
		wt/wt	wt/Dup	Dup/Dup	wt	Dup	*P* value
Purépechas	49	24 (49)	18 (38)	7 (14)	0.67	0.33	0.2487
Tarahumaras	97	50 (52)	37 (38)	10 (10)	0.71	0.29	0.4261
Huicholes	97	43 (45)	42 (43)	12 (12)	0.66	0.34	0.7265
Mayas	139	55 (58)	66 (37)	18 (6)	0.63	0.37	0.7948
Tének	97	47 (48)	40 (41)	10 (11)	0.69	0.31	0.7316
Nahua	213	89 (42)	103 (48)	21 (10)	0.66	0.34	0.2618
Mestizos[1]	306	177 (58)	112 (37)	17 (6)	0.76	0.24	0.8961

(1) Juaréz-Rendón et al. 2011.

P-02

GAUCHER'S DISEASE: EVIDENCE OF FOUNDER EFFECT IN A POPULATION FROM TABULEIRO DO NORTE, NORTHEASTERN BRAZIL

Chaves, R.G. [1,2†], Veiga Pereira, L.[3], Tófoli, F.[3], Rosemberg, R.[3], Fernandes Carvalho, M.D.[4], Carneiro Coelho, J.[5], Michellin-Tirelli, K.[6], de Freitas Chaves, M.[7], Cavalcante Junior, G.B.[8]

(1) Programa de Pós-graduação da UFRN – Natal – RN
(2) Secretaria Municipal de Saúde – Tabuleiro do Norte – CE
(3) Instituto de Biociências da Universidade de São Paulo – São Paulo – SP
(4) Universidade Estadual do Ceará – Fortaleza – CE
(5) Departamento de Bioquímica da ICBS – UFRGS – Porto Alegre – RS
(6) Serviço de Genética Médica do HCPA – UFRGS – Porto Alegre – RS
(7) Faculdade de Medicina da Unichristus – Fortaleza – CE
(8) Departamento de Análises Clínicas e Toxicológicas – CCS – UFRN

†Corresponding author: Rigoberto Gadelha Chaves; Rua Capitão José Rodrigues 4774, Centro, Tabuleiro do Norte, Ceará, Brazil. CEP 62960-000. Telephone: +55 88 88 09 91 97
E-mail: rigobertogadelha@hotmail.com

Introduction: High incidences of Mendelian diseases in isolated populations have been explained by the concept of "founder effect". Gaucher's Disease (GD) is caused by a β-glucocerebrosidase (GBA) deficiency leading to the accumulation of glucocerebroside in the reticuloendothelial system. Molecular analysis can predict the GD phenotype and is essential in genetic counseling. The prevalence of GD in Tabuleiro do Norte (1:4.000) is the highest in Brazil. The purpose of this study was to present evidence of a founder effect for GD in Tabuleiro do Norte based on enzyme and molecular analysis, and a genealogical survey. **Methods:** Between March 2009 and December 2010, 131 subjects at risk for GD (GBA in dried blood ≤2.19 nmol/h/mL) were submitted to analysis of GBA in leucocytes and molecular analysis. In addition, 5 confirmed GD patients from the same community were submitted to molecular analysis to characterize the genetic profile of the population. **Results:** Based on the enzymatic and molecular analysis, the subjects were classified into 3 categories: affected (n=5), carrier (n=20), and non-carrier (n=111). All carriers were G377S/+ and affected subjects were homozygous (G377S/G377S). The groups differed significantly with regard to enzyme activity: affected subjects displayed the lowest levels of GBA activity and the highest levels of chitotriosidase activity. **Conclusion:** The identification of a single type of mutation (G377S) in the entire sample (carriers and homozygotes from different families and generations), the history of the settlement and the results of the genealogical survey suggest a founder effect for GD in this population.

P-03

GBA MUTATIONAL SPECTRUM OF NEWLY DIAGNOSED HUNGARIAN PATIENTS WITH GAUCHER DISEASE

Juhász, P., Tóth, B., Csorba, G., Maródi, L., Erdős, M.†

Department of Infectious and Pediatric Immunology, University of Debrecen Faculty of Medicine, Debrecen, Hungary
†Corresponding author: Melinda Erdős, email: melinda.erdos@yahoo.com

Gaucher disease (GD) is an autosomal recessive storage disorder caused by mutations in the gene coding for the acid β-glucocerebrosidase (*GBA*). The mutational spectrum of Hungarian patients with GD was first published in 2007 (Blood Cells Mol. Dis., 39:119–123). Since then five more patients were genetically analysed in our LSD Center. Senger sequencing was used detect sequences of coding exons by using genomic DNA isolated from blood cells. We have found homozygous N370S mutation in 1 patient, compound heterozygous N370S/L444P sequence variants in 1 patient and compound heterozygous N370S/c.84dupG mutation in 2 patients. Prenatal genetic analysis was performed on the request of a mother with N370S/WT heterozygous mutation and we found an N370S/Rec*N*ciI compound heterozygous mutation in the fetus. Including genetic data of all the 31 patients we have analysed, the most frequent genotype in Hungary is the N370S/Rec*N*ciI found in 8 patients. The second most frequent mutation is N370S/L444P detected 6 patients followed by the c.N370S/c.84dupG in 3 patients. The most frequent alleles were the N370S (43,7%) and the Rec*N*ciI and L444P both 14%. We found missense mutations in 82%, splicing mutations in 6%, small deletions in 6% and duplications in 6% of *GBA*.

P-04

CLINICAL CONTEXT OF THE PATIENT WITH GAUCHER DISEASE: NOTHING IS UNIFACTORIAL

Paskulin, L.[1,2], Koppe, T.[1,2], Uribe Cruz, C.[3], Doneda, D.[4], Siebert, M.[1,5], Maffazzioli Santos, L.[6,7], Vairo, F.[1,8], Schwartz, I.V.D.[1,2,7,8]

[1]Medical Genetics Service, Hospital de Clínicas de Porto Alegre, Porto Alegre, RS, Brazil; [2]Universidade Federal do Rio Grande do Sul, Porto Alegre, RS, Brazil; [3]Post Graduation Program in Gastroenterology, Universidade Federal do Rio Grande do Sul, Porto Alegre, RS, Brazil; [4]LTD Laboratory, Nutrition Program, Medical School, Universidade Federal do Rio Grande do Sul, Porto Alegre, RS, Brazil; [5]Post Graduation Program in Cellular and Molecular Biology, Universidade Federal do Rio Grande do Sul, Porto Alegre, RS, Brazil; [6]Radiology Service, Hospital de Clinicas de Porto Alegre, Porto Alegre, RS, Brazil; [7]Post Graduation Program in Surgery, Universidade Federal do Rio Grande do Sul, Porto Alegre, RS, Brazil; [8]Post Graduation Program in Genetics and Molecular Biology, Universidade Federal do Rio Grande do Sul, Porto Alegre, RS, Brazil; [9]Department of Genetics, Universidade Federal do Rio Grande do Sul, Porto Alegre, RS, Brazil

Gaucher disease (GD) is the most common lysosomal disease, and it is associated with hyperferritinemia. Substrate reduction therapy (SRT) is one of the strategies available for GD treatment. However, diarrhea associated with inhibition of disaccharidases is the most common side effect.

OBJECTIVE: To report a GD type I patient with complex clinical presentation, culminated with apparent clinical worsening in use of SRT.

CASE REPORT: Female patient with GD type I, 42 years old, SSI= 5, had phlebotomy by hyperferritinemia prior to diagnosis. Patient started the SRT (+ low-carbohydrate/lactose diet) considering she had bone pain as the main clinical manifestation. Even so, the patient developed diarrhea alternating with constipation associated with weight loss, worsening of hyperferritinemia (with doubtfully increased hepatic iron through MRI) and no improvement in bone pain after one year of treatment. For these reasons, SRT was replaced by enzyme replacement therapy (ERT). Right after the beginning of ERT, strongyloidiasis was diagnosed by endoscopy, and non-persistency of lactase activity by DNA analysis. Ivermectin and a special diet for lactose intolerance were prescribed. After 6 months on ERT, the patient showed improvement in bone pain, abdominal symptoms, and hyperferritinemia.

DISCUSSION/CONCLUSIONS: Clinical and laboratory improvement of the patient may not be only due to the replacement of SRT to ERT. Before starting SRT, it is highly recommended to perform screening and treatment of comorbidities that possibly enhance intestinal adverse events associated with this modality of treatment.

P-05

GENOTYPE/PHENOTYPE DISCREPANCY IN GAUCHER DISEASE TYPE 3: CASE REPORT

Martins, A.M.[1], Curiati, M.A.[1]; Rand, M.[1]; Mendes, C.[1]

[1]Centro de Referência em Erros Inatos do Metabolismo, Universidade Federal de São Paulo

Background: Gaucher Disease (GD) is classically divided into 3 subtypes: nonneuronopathic type I, acute neuronopathic type II, and subacute neuronopathic type III. Type I is the most common and lacks primary CNS involvement. Types II and III have CNS involvement and neurologic manifestations.

Most prevalent mutations associated with the neuronopathic subtypes are: L444P, V394L, G377S and N188S. The N370S mutation is associated with the nonneuronopathic subtype, and has never been described before in a patient with the neuronopathic subtype.

Case Report: Female, 20y, diagnosed type 3 GD with 11y, presenting neurodevelopment delay since 1y, hepatosplenomegaly and pyramidal syndrome. Started ERT using Imiglucerase with 11y, presenting low platelet count during the period of Imiglucerase shortage. The patient developed psychomotor agitation and epilepsy, became unable to walk or talk, barely understands spoken words and lost sphincter control.

Beta-Glucocerebrosidase enzyme activity: 0,11 nmol/h/mg of protein (Reference 10 - 45), Brain MRI with non specific supratentorial white matter lesions. EEG showing Left Fronto-Central epileptiform activity. GBA Mutation Analysis: N370S/L444P+A456P.

Discussion and Conclusion: N370S mutation is frequent in homozygosity and in compound heterosigosity, and well known for causing a nonneuronopathic subtype, as shown by Fairley et all in 2008. L444P mutation was the first to be described associated with the neuronopathic subtypes. Grabowski et all (1997) stated that the presence of N370S in one allele is enough to diagnose a nonneuronopathic subtype (“protects” against the neuronopathic subtypes). This patient has one N370S mutation but her diagnostic is GD type3.

P-06

EVALUATION OF SINGLE NUCLEOTIDE POLYMORPHISMS IN *SCARB2*, *PSAP* AND *CLN8* GENES IN A GROUP OF BRAZILIAN PATIENTS WITH GAUCHER DISEASE

Siebert, M.[1], Vasata Furtado, G.[1], Saraiva-Pereira, M.-L.[1,2†]

[1]Laboratório de Identificação Genética – Centro de Pesquisa Experimental e Serviço de Genética Médica – Hospital de Clínicas de Porto Alegre; [2]Departmento de Bioquímica, Universidade Federal do Rio Grande do Sul, Porto Alegre, RS, Brazil

†Presenting author: Maria-Luiza Saraiva-Pereira; Medical Genetics Service – Hospital de Clínicas de Porto Alegre; Rua Ramiro Barcelos, 2350 – CEP 90035-903 – Porto Alegre – RS – Brazil; Email: mlsaraivapereira@gmail.com

Gaucher disease (GD), the most common lysosomal storage disorder, is caused by glucocerebrosidase deficiency (GCase, E.C. 3.2.1.45) due to mutations in the *GBA1* gene. Similar to many single-gene diseases, few genes have been described as potential modifiers of GD phenotypes, including *SCARB2*, *PSAP,* and *CLN8*. The aim of this work was to evaluate the association of *SCARB2*, *PSAP*, and *CLN8* genes in a group of Brazilian GD patients through targets single nucleotide polymorphisms (SNPs). A total of seven SNPs were selected and evaluated in DNA samples from 134 patients and 100 controls. Allelic and genotypic frequencies were established in both patients and control groups. T/T genotype in rs2070968 (*PSAP* gene) was found only among GD patients that are homozygous for the N370S mutation. Significant association between the intronic *SCARB2* SNP (rs6532244) and GD was also shown, with higher frequency of the A/A genotype in patients than in controls. A significant difference between N370S/N370S GD patients and those with a different *GBA1* genotype was observed when considering the rs7008465 variant. In this case, G allele was more common among patients carrying N370S mutation in both alleles, being possibly associated to the protective effect against neurological damage as previously suggested. The associations reported here raise novel insights into the role of these candidate genes as modifiers of GD phenotypes. Additional studies are essential to replicate such findings, and further functional studies are important to demonstrate the proper physiological role of those sequence variants (Supported by CNPq and CAPES).

P-07

IDENTIFICATION OF THE ACID/BASE AND NUCLEOPHILE IN ALL HUMAN RETAINING BETA-GLUCOSIDASES

Kallemeijn, W.W.[a], Witte, M.D.[b, c], Voorn-Brouwer,T.M.[a], Walvoort, M.T.C.[b, d], Li, K-Y.[b], Codée, J.D.C.[b], van der Marel, G.A.[b], Boot, R.G.[a], Overkleeft, H.S.[b] and Aerts, J.M.F.G.[a, 1]

[a]Department of Medical Biochemistry, Academic Medical Center, University of Amsterdam, Meibergdreef 15, 1105 AZ Amsterdam (The Netherlands). [b]Bio-organic Synthesis, Leiden Institute of Chemistry, P.O. box 9502, 2300 RA Leiden (The Netherlands). [c]Current address: Bio-Organic Chemistry, Stratingh Institute for Chemistry, University of Groningen, Nijenborgh 7, 9747 AG Groningen (The Netherlands). [d]Current address: Department of Biology and Department of Chemistry, Massachusetts Institute of Technology, 77 Massachusetts Avenue, Cambridge, MA 02139 (USA)

Retaining β-exoglucosidases operate by a mechanism in which the key amino acids driving glycosidic bond hydrolysis act as catalytic acid/base and nucleophile. Recently we designed two distinct classes of fluorescent cyclophellitol-type activity-based probes (ABPs) that exploit this mechanism to covalently modify the nucleophile in retaining β-glucosidases. Where cyclophellitol β-epoxide ABPs require a protonated acid/base for irreversible inhibition, β-aziridine ABPs do not. Here we illustrate the use of ABPs to unambiguously identify the acid/base and nucleophiles in the four known retaining β-glucosidases in man. After site-directed mutagenesis of residues putatively involved in the reaction mechanism, rescue of enzymatic activity with sodium azide enables the identification of catalytic residues. Subsequently the identity of the acid/base and nucleophile is made using ABPs. The method was validated on glucocerebrosidase (GBA, CAZy glycosylhydrolase family GH30) and then applied to non-homologous (putative) β-glucosidases from GH1: GBA3, LPH, klotho, βklotho and KLPH. Finally, we identified the acid/base and nucleophile in β-glucosidase GBA2 (GH116), recently implicated in apoptosis, oncogenesis and neurological disorders.

P-08

ACTION MYOCLONUS-RENAL FAILURE SYNDROME: DIAGNOSTIC APPLICATIONS OF ACTIVITY-BASED PROBES AND LIPID ANALYSIS

Gaspar, P.[1,2] , Kallemeijn, W.W.[2], Strijland, A.[2] , Scheij, S.[2] , Van Eijk, M.[2] , Aten, J.[3] , Overkleeft, H.S.[4] , Balreira, A.[1] , Zunke, F.[5], Schwake, M.[6], Miranda, C. S.[1] and Aerts, J.M. F. G.[2]

[1] Lysosome and Peroxisome Biology Unit (UniLiPe), Institute of Molecular and Cell Biology (IBMC), University of Oporto, Oporto, Portugal; [2]Department of Medical Biochemistry, Academic Medical Center, Amsterdam, The Netherlands; [3]Department of Pathology, Academic Medical Center, Amsterdam, The Netherlands; [4]Department of Bioorganic Chemistry, University of Leiden, The Netherlands; [5]Department of Biochemistry, Christian Albrechts Universitat Kiel, Kiel, Germany; [6]Department of Biochemistry, University of Bielefeld , Bielefeld, Germany

Lysosomal integral membrane protein-2 (LIMP2) mediates trafficking of glucocerebrosidase (GBA) to lysosomes. Deficiency of LIMP2 causes action myoclonus-renal failure syndrome (AMRF). LIMP2-deficient fibroblasts virtually lack GBA like the cells of patients with Gaucher disease (GD), a lysosomal storage disorder caused by mutations in the GBA gene. While GD is characterized by the presence of glucosylceramide-laden macrophages, AMRF patients do not show these. We studied the fate of GBA in relation to LIMP2 deficiency by employing recently designed activity-based probes labeling active GBA molecules. We demonstrate that GBA is almost absent in lysosomes of AMRF fibroblasts. However, white blood cells contain considerable amounts of residual enzyme. Consequently, AMRF patients do not acquire lipid-laden macrophages and do not show increased plasma levels of macrophage markers, such as chitotriosidase, in contrast to GD patients. We next investigated the consequences of LIMP2 deficiency with respect to plasma glycosphingolipid levels. Plasma glucosylceramide concentration was normal in the AMRF patients investigated as well as in LIMP2-deficient mice. However, a marked increase in the sphingoid base, glucosylsphingosine, was observed in AMRF patients and LIMP2-deficient mice. Our results suggest that combined measurements of chitotriosidase and glucosylsphingosine can be used for convenient differential laboratory diagnosis of GD and AMRF.

P-09

A MODIFIED METHOD FOR THE DETERMINATION OF ACID BETA-GLUCOSIDASE IN DRIED BLOOD SPOT SAMPLES AS A DIAGNOSTIC APPROACH IN THE ANDEAN COUNTRIES: PRELIMINARY RESULTS

Pacheco, N.*[1] & Uribe, A.*[2]
*Centro de Investigaciones en Bioquímica, Facultad de Ciencias, Universidad de los Andes, Bogotá, Colombia; [1]Presenting author; Research Assistant, nm.pacheco27@uniandes.edu.co
[2]Co-author; Director of Centro de Investigaciones en Bioquímica and assistant professor at Universidad de los Andes. jeuribe@uniandes.edu.co

The deficiency of acid beta-glucosidase (bglu) causes Gaucher disease. Diagnosis is usually made evaluating bglu enzymatic activity in leukocytes. Using dried blood spot samples (DBS) in the diagnostic approach is advantageous given the difficult geographic conditions in the Andean countries. We used an enzymatic technique (Chamoles et al.,2001) that represented a challenge in some patients showing an over-expression of bglu isoforms. Additionally, the test is susceptible to false negatives, making difficult to identify some patients. We propose a modified DBS method for diagnostic approach of patients with Gaucher disease.

Methods

We evaluated 32 subjects diagnosed with Gaucher disease and 22 healthy subjects. Using 4-methylumbelliferyl-D-glucopyranoside as substrate and punches of 6mm, 60ul of eluted sample were placed in 96-well plates. A bglu isoforms' inhibitor (conduritol-b-epoxide) was used to avoid false negatives. We incubated plates for 3 hours and evaluated Chitotriosidase (ChT) to support the diagnostic approach in patients who haven't the 24bp duplication in ChT gene.

Results

Conduritol-b-epoxide inhibited bglu isoforms in 90-95% at pH 5.2. This allowed us to detect 1 Peruvian patient with isoform over-expression. We also reduced the incubation time (3 hours). Chamoles' method showed low correlation ($p>0.05$) but the new technique evidenced significant results ($p=0.01$, Pearson coefficient=0.45) when comparing DBS and leukocyte results. Twenty-six patients had increased ChT activity (range:101.6-2204.78nmol/ml/h, VR<94nmol/ml/h). Six showed reduced or null activity (range:0-63.47nmol/ml/h). Bglu activity ranged from 0.39 to 3.88nmol/ml/h in patients and 4.64 to 10.99nmol/ml/h in controls. Correlation suggest that this method could be useful to diminish the false negative rate.

P-10

MONOCYTE RESPIRATORY BURST CAPACITY AND LYMPHOCYTE SUBSETS IN GAUCHER TYPE 1 PATIENTS

Rodic, P.[1†], Janic, D.[1, 5], Popadic, D.[3], Suvajdzic Vukovic, N.[2, 5], Kraguljac Kurtovic, N.[2], Djordjevic, M.[4, 5], Mitrovic, M.[2]

[1] University Children's Hospital, Belgrade, Serbia
[2] Clinic of Hematology, Clinical Center of Serbia, Belgrade, Serbia
[3] Institute of Immunology, School of Medicine, University of Belgrade, Serbia
[4] Mother and Child Healthcare Institute, Belgrade, Serbia
[5] School of Medicine, University of Belgrade, Serbia
† Presenting author: dr Predrag Rodic, MSc; Department of Hematology and Oncology; University Children's Hospital, Tirsova 10, 11000 Belgrade, Serbia; Email: predrag.rodic@udk.bg.ac.rs

Background: It is assumed that Gaucher patients may be prone to infections due to defective neutrophil function. Since macrophages are the main cell type affected in Gaucher disease, our aim was to determine the contribution of these cells to susceptibility to infection by studying respiratory burst capacity of peripheral blood monocytes. Additionally, we analyzed distribution of peripheral blood lymphocyte subsets in a group of Gaucher type I patients.
Methods: Respiratory burst analysis was performed in eleven Gaucher type 1 patients and eleven control subjects using flow cytometry, measured as dihydrorhodamine-123 (DHR) mean fluorescence after phorbol 12-myristate 13-acetate stimulation. Lymphocyte subsets were enumerated by flow cytometry in thirty type I Gaucher patients and compared to twenty healthy control subjects.
Results: There was no statistical difference in the mean DHR fluorescence among the patients and respective controls. Also, statistical difference was not reached among patients treated with enzyme replacement treatment at the time and those untreated. The patients had significantly lower count of white blood cells, total lymphocytes, T lymphocytes, $CD4^+$ and $CD8^+$ lymphocytes, as well as natural killer cells comparing to normal control subjects. Enzyme replacement treatment, scored severity of the disease and chitotriosidase level did not affect significantly the tested cell counts.
Conclusions: Respiratory burst disturbance in monocytes does not seem to contribute to increased susceptibility to infection in Gaucher patients. Lymphopenia in Gaucher patients is due to selective T-cell and NK-cell cytopenia irrespective of disease severity as well as replacement treatment.

P-11

ROLE OF RED BLOOD CELL ON THE PATHOPHYSIOLOGY OF GAUCHER DISEASE AND EFFECT OF THE ENZYME REPLACEMENT THERAPY

Franco, M.[1-4†], Marin, M.[1-4], Reihani, N.[1-4], Collec, E.[1-4], Billette de Villemeur, T.[5,6], Rose, C.[6,7], Mignot, C.[5,6], Colin, Y.[1-4], Belmatoug, N.[6,8] & Le Van Kim, C.[1-4]

[1]Inserm U1134, Paris, France; [2]Université Paris Diderot, Sorbonne Paris Cité, UMR_S 1134, Paris, France; [3]Institut National de la Transfusion Sanguine, Paris, France; [4]Laboratoire d'excellence GR-Ex, Paris, France; [5]Service de Neuropédiatrie, Hôpital Trousseau, Assistance Publique–Hôpitaux de Paris and Université Pierre et Marie Curie, Paris, France; [6]Centre de Référence des Maladies Lysosomales, Clichy, France; [7]Service d'Hématologie et de cardiologie Hôpital Saint Vincent de Paul, Université Catholique de Lille, Lille; [8]Service de Médecine Interne, Hôpital Beaujon, Clichy, France;
†Corresponding author: melanie.franco@inserm.fr

Gaucher disease (GD) is a lysosomal storage disorder, impairing glucosylceramide catabolism. Glucosylceramide-laden macrophages are responsible for the major clinical signs of GD (thrombocytopenia, organomegaly, bone disease). However, other symptoms of the disease such as anemia, vascular occlusion and spleen and bone infarcts might involve red blood cells (RBCs). Our previous findings uncover a new aspect in GD showing that GD RBCs exhibited abnormal rheological, morphological, and membrane adhesion properties (*Franco et al. 2013, Blood*).

To determine whether GD enzyme replacement therapy (ERT) normalizes RBC parameters, we compared RBCs morphology and rheology between 3 groups : healthy volunteers (CTR Group), untreated naïve GD patients (UT Group) and Velaglucerase treated-patients Group (Velaglucerase Group). Longitudinal studies were performed on 4 GD patients followed during 2 years before and after the beginning of ERT.

RBC morphology was examined on Giemsa-stained peripheral blood smears. As previously, we observed a higher proportion of abnormal RBC shapes in UT Group compared with CTR Group. Hemorheologic measurements were performed by laser diffraction analysis. We confirmed a reduced Elongation Index at low shear in UT Group. Among the 3 groups and the longitudinal study, we observed that Velaglucerase seems to restore normal morphology and deformability of GD RBCs. We have to confirm these data with higher number of patients and to investigate other RBCs properties such as adhesion.

Altogether, our preliminary data indicate that some GD RBCs properties might be target of ERT and new marker of treatment efficiency.

This work was supported in part by grants from Shire

P-12

GAUCHEROMAS: WHEN MACROPHAGES PROMOTE TUMOR FORMATION AND DISSEMINATION

Goker-Alpan, O.[1†], Limgala, R.P.[1], Ivanova, M.[1], Hebert, A.[1], Komlodi-Pasztor, E.[1], Elstein, D.[2], Rosenbaum, H.[3], Zimran, A.[2]

[1]Lysosomal Disorders Treatment Unit, Fairfax, VA, USA[2] Shaare Zedek Medical Center, Jerusalem, Israel' [3] Rambam Medical Center, Haifa, Israel
†Presenting author's details: Ozlem Goker-Alpan,M.D; Lysosomal Disoders Unit, O&O Alpan, LLC, Fairfax, VA; Email address: ogokeralpan@oandoalpan.com

Background: Solid and non-solid tumors are described in patients with Gaucher disease. Of those, Gaucheromas are caused by tumor-like deposition of Gaucher-cells, and are not only a diagnostic curiosity without certain etiology, but also a therapeutic challenge, as they are refractory to medical intervention. Gaucheromas occur in liver and spleen, rarely originate within bone; Gaucheromas arising at other sites are limited to case reports
Cases and Methods: Three females and one male (18-57 years) with Gaucher disease (genotypes: L444P/L444P, N370S/N370S) were diagnosed with extraosseous-Gaucheromas. Three were treated (ERT/SRT); one was Gaucher treatment-naïve. One presented with osseous Gaucheroma, subsequently T8-L1 para-spinal; two had pelvic masses. The male patient had a retroperitoneal mass adjacent to the kidney. To study underpinnings of Gaucheromas, flowcytometry-based immuno-phenotyping was used on PBMCs, and tissue samples were evaluated with immunohistochemistry/immunofluorescent techniques.
Results: Peripheral blood was positive for monocyte markers CD14, CD16, and M2 marker CD163 chemokine receptor CCR4. Increased numbers of non-classical monocytes ($CD14^{low}/CD16^{hi}$) were observed. The CD163 fraction among classical and non-classical monocytes was similar to Gaucher-controls, however only the patient with Gaucheroma showed CCR4+ non-classical monocytes. Tumor tissue was infiltrated with Gaucher-type cells, demonstrating reactivity against CD163, CD 68, M2 macrophage marker, and VEGF, a pro-neoplastic angiogenesis factor. Cell proliferation marker Ki67 and tumor chemo-attractant CCL2 were negative.
Discussion: Gaucheroma cells exhibit characteristics of tumor–associated-macrophages (TAM), major players in cancer-related inflammation. Occurrence of this specialized monocyte subset in the peripheral blood may be the underlying cause for macrophage homing in Gaucheroma formation and dissemination.

P-13

FALSE NEGATIVE RESULT IN B–GLUCOSERBROSIDASE ASSAY OF A GAUCHER'S DISEASE PATIENT WITH PLASMA CELL LEUKEMIA.

Deutsher-Chertkow, Y.[1]; Zhilin-Roth, A.[1]; Chen Zion, Y.[2]; Sarig, G.[1]; Rosenbaum, H.[2]

[1]Hematology Laboratory, Rambam Health Care Campus, Haifa, Israel;
[2]Department of Hematology and Bone Marrow Transplantation, Rambam Health Care Campus, Haifa, Israel

Background Measurement of β–Glucocerebrosidase activity is an essential step in Gaucher's disease (GD) diagnosis. Here we report a case of a false negative result in β–Glucocerebrosidase test, probably due to comorbidity of GD with plasma cell leukemia (PCL).

Methods: Activities of β–Glucocerebrosidase in mononuclear cells and of serum chitotriosidase were measured using 4-Methylumbelliferyl–β–D–Glucopyranoside and 4-Methylumbelliferyl-β-D-NNN-Triacetyl-Chitotriose substrates, respectively. Free light chains concentrations were quantified using Freelite kit (TBS).

Results: Type 1 GD patient (c.1226A>G; p.N370S) after partial splenectomy and under chronic Cerenzyme treatment, was recently diagnosed with free lambda PCL. Unexpectedly, normal β–Glucocerebrosidase activities (15.2 and 16.4nM/hour/mg) were measured in the presence of blood plasma cells (PC) ($57x10^3$/□l; 78% and $1.2x10^3$/□l; 10%) within 10 days of treatment with Velcade, Cytoxan and Dexacort. A follow-up sample, two months later, without PC, showed low enzymatic activity (4nM/hour/mg), in line with GD pathology. Free lambda levels were reduced in parallel to PC decrease (from 3770mg/l to 74mg/L). Chitotriosidase activity was moderately elevated all over this period (800-1000nmole/hr/ml).

Conclusion:

To our knowledge, this is the first report of a false negative result in β–Glucocerebrosidase biochemical assay. Previous studies have shown that not only monocytes, but also lymphocytes and platelets exhibit β–Glucocerebrosidase activity. Thus, we speculate the presence of PC may contribute to the total β–Glucocerebrosidase activity measured in this patient and could mask the pathological deficiency. Further research is required to study β–Glucocerebrosidase activity in isolated plasma cells and in patients with PCL.

P-14

PROINFLAMMATORY PROFILE BETWEEN MULTIPLE MYELOMA AND GAUCHER DISEASE

Gervas-Arruga, J. [1,2,3,4†], Andrade, M.[1,2,3,4,5], Giraldo, P.[1,2,3,4,5]

[1]Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER); [2]Translational Research Unit, Miguel Servet University Hospital, Zaragoza; [3]Spanish Gaucher Disease Foundation (FEETEG),Zaragoza; [4]IACS, Zaragoza; [5]Hematology Department, Miguel Servet University Hospital, Zaragoza, Spain

†Presenting contact author: Javier Gervás Arruga; Translational Research Unit, Miguel Servet University Hospital, Zaragoza, Spain; e-Mail: gervas.j@gmail.com

Introduction: Several studies have reported an increased incidence of MGUS and multiple myeloma (MM) in patients with type 1 Gaucher disease (GD) (3.5 times). Immune system deregulation resulting from glucocerebroside accumulation, may influence the development of hematologic malignancies. However, the pathological mechanisms that influence MM development in GD1 patients is unknown. Cytokines produced in response to glucocerebroside accumulation, may be a critical factor in explaining the pathogenesis of MM in GD. This cytokine environment could trigger lymphocyte expansion and ultimately transformation.

Aim: To analyze and compare a proinflammatory cytokine profile among MGUS; MM and GD1 patients.

Methods: A panel of cytokines: IL4, IL6, IL7, IL10, IL13, MIP1α, MIP1β and TNFα were analyzed in plasma samples by Luminex®100 platform and Millipore cytokine kits in a 36 MGUS patients (females 58,3%, mean age: 75 years; range: 53-89); 49 MM patients (females 42%, mean age: 68 years; range: 39-89) and 38 GD1 patients (females 36,8%, mean age: 39,2 year; range: 7-79) from Hematology Department; FEETEG registry, and 71 healthy controls. Data were analyzed using Mann-Whitney-U and Kruskall-Wallis.

Results: Significant differences ($p<0.05$) in IL4; MIP-1α; MIP-1β and TNFα values were found between controls; MGUS; MM and GD1 patients and also IL13 in MM and GD1. MM and GD1 not showed differences in the median values of IL4 and IL13. MM and GD1 groups showed significant differences in MIP-1α, MIP-1β and TNFα values.

Conclusions: These results support that GD1 and MM patients share similar proinflammatory profiles and could justify the appearance of hematologic malignancies in GD1 patients.

This work was partially financed by FIS and Fundación Española para el Estudio y Terapéutica de la Enfermedad de Gaucher (FEETEG) y otras lisosomales and Fundación para el Estudio de la Hematología y Hemoterapia en Aragón (FEHHA).

P-15

CLINICAL COURSE OF TWO PATIENTS WITH GAUCHER DISEASE, MGUS AND MULTIPLE MYELOMA

Donner, M.G., Santosa, D., Häussinger, D., vom Dahl, S.

Department of Gastroenterology, Hepatology and Infectious Diseases, University of Düsseldorf, Moorenstrasse 5, D-40225 Düsseldorf, Germany

Background: Patients with Gaucher disease carry an increased risk of monoclonal gammopathy of undetermined significance (MGUS) and myeloma. There are only few data on the clinical course of myeloma in patients with this lysosomal storage disease. In a cohort of approximately 80 patients, we report on two patients with this condition, one of whom underwent successful autologous stem cell transplantation.

Case reports: A male patient, *1946, was diagnosed having Gaucher disease type I at the age of 39. One year later, enzyme replacement therapy (ERT) with imiglucerase (25 U/kg body weight be-weekly) was started. Eight years after initiating ERT, MGUS was diagnosed. One year later, Ig concentration had further increased. The patient underwent bone marrow aspiration and was found to have progressed to myeloma (IgG κ, stage Ia, 20 % bone marrow infiltration and osteolytic lesions in the thoracic spine). Close hematologic follow-up showed a progression of one osteolytic lesion 18 months after the diagnosis was made. Subsequent treatment with radiation, dexamethasone and biphosphonates was initiated, followed by chemotherapy with vincristine, doxorubicin and cyclophosphamide. Within 3 months progressive osteolyses became apparent, necessitating chemotherapy with ifosfamide, epirubicin and etoposide, followed by stem cell apheresis, conditioning and autologous stem cell transplantation. After three months, conditioning and autologous stem cell transplantation had to be repeated and partial remission of myeloma was achieved. On progression of myeloma and during the first CTX there was a sharp rise in chitotriosidase activity (2.858 nmol/(ml x h), normal range < 100). Subsequently imiglucerase was increased to 60 U/kg body weight biweekly. Gaucher disease remained stable during the period of autologous cell transplantation and chitotriosidase activity was < 1000 nmol/(ml x h) after 11 months of treatment. Three years after autologous stem cell transplantation the patient is in a good clinical condition with myeloma constantly being in partial remission and stable parameters of Gaucher disease.

A female patient, *1948, was diagnosed with GD at the age of 46 years, subsequent to bone marrow smears because of hepatosplenomegaly and anemia with low platelets. GBA activity and genotyping (N370S homozygote) had confirmed the diagnosis of type I Gaucher disease. MGUS was present from the beginning, with normal total protein (TP), but IgA type □ being elevated to 1050 mg/dl (normal 70-400) at baseline. Enzyme replacement therapy with alglucerase/imiglucerase at a dose of 30 IU/kg body wt. e.o.w. was installed, IgA and MGUS being stable. After an unremarkable clinical course for 17 years, the patient delevoped symmetric pale/blue discoulorations of her distal hand skins, night sweats and exertional dyspnea. While TP was still normal, IgA concentration had increased during 1-2 years to 1355 and 1585 mg/dl, respectively, and bone marrow smears showed 40 % bone marrow infiltration by plasma cells and the diagnosis of multiple myeloma stage Ia was made. MR did not reveal new osteolytic lesions and chitotriosidase activity was 3120 nmol/(ml x h). The patient is now awaiting standard chemotherapy.

Discussion: In conclusion, close metabolic follow-up and adjustment of therapy resulted in a stable clinical course of Gaucher disease in a patient with myeloma undergoing autologous stem cell transplantation. The other patient awaits standard multiple myeloma therapy with conditioning and autologous stem cell transplantation being planned on the long term. Results from the literature show encouraging responses in patients who suffer from Gaucher-associated multiple myeloma. They usually have no major inflicting comorbidities and the myeloma is - due to close monitoring of these patients - often diagnosed at a relatively early stage.

P-16

BRAZILIAN PATIENTS WITH GAUCHER DISEASE PRESENT INCREASED SERUM β_2-MICROGLOBULIN

Koppe, T.B.[1;2], Heineck, B.L.[1;2], Paskulin, L.D.[1], Camargo, M.B.[1], Doneda, D.[1;3], Donis, K.C.[4;6], Vairo, F.[1;2;4], Daudt, L.E.[1;4;5], Schwartz, I.V.[1;4;6]

[1]Universidade Federal do Rio Grande do Sul – UFRGS –, Porto Alegre, Brazil;
[2]Programa de Pós-graduação em Genética e Biologia Molecular, UFRGS, Porto Alegre, Brazil;
[3]Programa de Pós-graduação em Medicina: Ciências Médicas, UFRGS, Porto Alegre, Brazil;
[4]Hospital de Clínicas de Porto Alegre – HCPA –, Porto Alegre, Brazil;
[5]Serviço de Hematologia Clínica e Transplante de Medula Óssea, HCPA, Porto Alegre, Brazil;
[6]Serviço de Genética Médica, HCPA, Porto Alegre, Brazil

Multiple myeloma (MM) is prevalent in Gaucher disease (GD), and presents β2-microglobulin (B2M) as biomarker. However, no studies have evaluated B2M in GD patients. This study aims at evaluating B2M levels in GD patients seen at a Reference Center located at Southern Brazil. A retrospective chart review was carried out. Two B2M measures were considered: a "baseline" (performed in 2011) and a "post-baseline" (the most current available on the database). Serum B2M reference range assumed was 600-2450 ng/mL. Thirty-five patients were included: 16 men; 18 p.N370S/p.L444P; 32 type 1-GD; median age at onset of treatment=22 years [3-61], and median treatment time= 9 years [1-19] (22 imiglucerase; 5 taliglucerase alfa; 2 eliglustat; miglustat 1 and 4 untreated). The median time between baseline and post baseline values was 1.63 months [0.32-2.11]. At baseline, 15/35 patients had levels of B2M above the reference range (median= 2222 ng/mL [1465-4630]) and, at the post-baseline, 8/26 patients (median= 2100.50 ng/mL [1151-5539]; p=0.052, n=26). There is no significant correlation between B2M levels and time of treatment (p=0.142); age (p=0.311); leukocytes (p=0.562); serum ferritin (p=0.075); chitotriosidase (p=0.100); and transferrin saturation (p=0.210). Concluding, B2M is frequently elevated in GD. Because GD is a risk factor for MM and B2M is a prognostic marker in MM, monitoring BM2 could be a way to assess the development risk of MM.

Keywords: Gaucher disease; β_2-microglobulin; multiple myeloma

P-17

RELATIONS BETWEEN AUTOPHAGY, LYSOSOMAL PERMEABILIZATION AND LYSOSOMAL STORAGE

Pupyshev, A.B.

Novosibirsk State Medical University, Novosibirsk, Russia

Autophagy is normally involved in cell response to lysosomal storage that includes accumulation autophagolysosomes and autophagosomes, inhibition of acid vesicle fusion, accumulation of non-completed autophagosomes (autophagosomal debris) (Ballabio, Gieselmann, 2009; Raben et al., 2010). Usually it is accompanied by lysosomal membrane permeabilization (capable to induce apoptosis - Pupyshev, 2011), and there are data that inhibition of autophagy decreases the permeabilization and cell death (Hsu et al., 2009).
Lysosomal storage diseases (GD, MSD, MPS IIIA, CLN) results in slower degradation of invaded exogenic aggregate-prone proteins (mutant huntingin and α-synuclein), accumulation of endogenous substrates of autophagy (ubiquitinated proteins, damaged mitochondria) (Settembre et al., 2008; Thelen et al., 2012; Xu Y.H. et al., 2014). This defect of autophagic flow leads to wrong quality control, accumulation of toxic proteins and damaged mitochondria generating reactive oxygen species (Osellame, Duchen, 2014). In some cases autophagic and proteasomal degradation of protein seems to be mutually compensatory processes. When proteasomal degradation is suppressed, autophagy can be activated and maintains needed rate of protein renewal (Pandey et al., 2007). But in LSD (autophagic flux inhibition) the proteasomic (compensatory) way seemingly is not able to eliminate the abundant protein/cytoplasm debris generated. However autophagy was found as a protective mechanism in some LSD (Nascimbeni et al., 2012) Another therapeutic approach is stimulation of discharge of storage vesicle by TFEB in GD, Pompe disease and other LSD that render already a positive therapeutic effect and weakening of autophagosome accumulation and lysosomal storage (Feeney et al., 2013).

P-18

GLYCOPROTEIN NONMETASTATIC MELANOMA PROTEIN B IS A SENSITIVE MARKER FOR LYSOSOMAL LIPID OVERLOAD IN MACROPHAGES

Lizama, Tanit., Marques, A.[1], Tol, M.[1], Ottenhof, R.[1], van Roomen , C.[1], Aten, J.[2], Claessen, N.[2], Argmann, C.[1], Aerts, J.M.F.G.[1], van Eijk, M.[1]

Departments of [1]Medical Biochemistry and [2]Pathology, Academic Medical Center, University of Amsterdam, The Netherlands. Email: m.c.vaneijk@amc.uva.nl

During obesity adipose tissue macrophages (ATM) have to scavenge and handle an increased lipid load. As adipocyte dysfunction occurs large amounts of lipids are spilled, which consequently will impact on macrophages and their lysosomes. The glycosphingolipidoses are also characterized by increased lipid accumulation, but these are a result of defects in the degradation machinery caused by enzyme deficiencies, absence of transport molecules or lack of activator proteins.

Recently we found that during obesity glycoprotein nonmetastatic melanoma protein B (Gpnmb) is induced several hundred fold in ATM in epididymal white adipose tissue. In addition we found Gpnmb to be induced in plasma of lysosomal storage disorders such as Gaucher Disease (GD).

Using the macrophage cell line RAW 264.7 it was found that Gpnmb induction occurs independent of cytokines, hypoxia and ER stress. Interestingly, palmitate, lysosomal stressors such as chloroquine, bafilomycin and concanamycin and inhibition of mTORC1 kinase activity by Torin1 all induce Gpnmb in a MITF-dependent manner. Furthermore, Gpnmb potentiates the induction of arginase-1, suggesting a role in tissue remodelling.

We postulate that aberrant lipid sensing provokes lysosomal stress, which triggers MITF-dependent gene transcription including Gpnmb. Gpnmb serves as a very sensitive reporter molecule of lysosomal dysfunction and is a potential biomarker for GD.

P-19

THE PROGNOSTIC VALUE OF THE SERUM FERRITIN LEVELS IN GAUCHER DISEASE

Koppe, T.B.[1;2], Heineck, B.L.[1;2], Paskulin, L.D.[1], Camargo, M.B.[1], Doneda, D.[1;3], Donis, K.C.[4;6], Vairo, F.[1;2;4], Daudt, L.E.[1;4;5], Schwartz, I.V.[1;4;6]

[1]Universidade Federal do Rio Grande do Sul – UFRGS –, Porto Alegre, Brazil;
[2]Programa de Pós-graduação em Genética e Biologia Molecular, UFRGS, Porto Alegre, Brazil;
[3]Programa de Pós-graduação em Medicina: Ciências Médicas, UFRGS, Porto Alegre, Brazil;
[4]Hospital de Clínicas de Porto Alegre – HCPA –, Porto Alegre, Brazil;
[5]Serviço de Hematologia Clínica e Transplante de Medula Óssea, HCPA, Porto Alegre, Brazil;
[6]Serviço de Genética Médica, HCPA, Porto Alegre, Brazil

Hyperferritinemia in Gaucher disease (GD) displays controversial utility. The objective was to evaluate serum ferritin (SF) and other laboratory tests of GD patients followed at the Reference Center for Gaucher Disease of Rio Grande do Sul, Brazil. Pre- (the most current prior to initiation of therapy) and post-therapy data (the most current) was compared in a retrospective chart review study. Values are expressed as absolute frequency or median [25th-75th percentiles]. α=0.05. Thirty-eight patients were included (18 men; 35 type 1-GD; 21 p.N370S/p.L444P and 7 splenectomized). Current age=31 [22-47] and total treatment time=9 [2-14] years (24 imiglucerase; 5 taliglucerase alfa; 2 eliglustat; 1 miglustat; velaglucerase alfa 1 and 5 without therapy). No patient had biochemical evidence of iron overload. Hyperferritinemia was presented in 14 patient pre-therapy and 12 patients in the post-therapy period. In the post-therapy period, transferrin saturation (%) increased from 19.25 [14-32] to 28.15 [23-35] (p=0.138, n=10) and serum iron (mg/dL) from 56 [46-89.5] to 91 [72.5-99] (p=0.126, n= 8). SF (ng/mL) decreased from 811 [614-1544] to 528 [439-653] in males and from 329 [190-1174] to 243 [123-710] in females. Considering both sexes, therapy reduced SF from 756 [318-1442] to 521 [227-655] (p=0.025, n=18). SF strongly correlated with age (pre-: ρ= 0.886, n=19, p<0.001 / post-therapy: ρ=0.537; n=37, p=0.001). Concluding, there was evidence of low transferrin saturation, despite the hyperferritinemia. SF was higher in males and elderly people. Therapy decreases SF along with clinical laboratory improvement (including serum iron and transferrin saturation). Thus, the reduction of SF probably reflects a favorable clinical outcome.

Keywords: Gaucher disease; hyperferritinemia; iron metabolism

P-20

ORIGIN OF PLASMA GLYCOSPHINGOLIPIDS: INVOLVEMEMNT OF ABCA1

Ghauharali-van der Vlugt, K.[1], Kallemeijn, W.[1], Scheij, S.[1], Ottenhoff, R.[1], P. A. A. van Roomen, C.[1], Vergeer, M.[2], Motazacker, M.[2], Groen, A.K.[3], Aerts, J.M. F.G.[1], and Groener, J.E.M.[1]

[1]Department of Medical Biochemistry, [2]Department of Vascular Medicine, Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands; [3]Department of Pediatrics/Laboratory Medicine, University Medical Center Groningen, Groningen, the Netherlands

Glycosphingolipids (GSLs) are in serum associated with lipoproteins including HDL. Given the involvement of ATP-binding cassette protein A1 (ABCA1) in efflux of (lipid raft associated) cholesterol and subsequent formation of HDL, a possible essential role for ABCA1 in efflux of GSLs was investigated.

We found that when ABCA1 is (partially) absent in humans or mice, plasma concentrations of GSLs are reduced similarly to cholesterol concentration. Plasma ceramide concentration on the contrary, was relatively unchanged. In the presence of apolipoprotein A-1, cellular efflux of all detectable SLs from control fibroblasts was demonstrable and to a lower extent efflux of ceramide. In fibroblasts from Tangier disease (TD) patients, GSL efflux is reduced but not that of ceramide. Furthermore, inhibition of ABCA1-mediated cholesterol efflux by probucol decreases GSL efflux and induction of ABCA1-mediated cholesterol efflux by C2-ceramide increases GSL efflux. In murine liver, a major site of HDL synthesis, ABCA1 deficiency did not result in accumulation of (G)SL or cholesterol. Instead, impaired efflux of these lipids led to down-regulation of genes involved in the rate-limiting steps of (G)SL and cholesterol synthesis.

In conclusion, the combined results of our study show that efflux of GSL from cells is largely ABCA1 dependent and suggesting that the HDL pathway is a major contributor to plasma GSL. Secondly, ceramide secretion into the blood via this pathway is of minor importance. Thirdly, GSL efflux is coupled to cholesterol efflux to HDL.

P-21

α-SYNUCLEIN DIMERIZATION IN ERYTHROCYTES OF GAUCHER DISEASE PATIENTS IN RELATION TO LIPID ABNORMALITIES AND OXIDATIVE STRESS

Moraitou, M.[1], Dermentzaki, G.[2], Dimitriou, E.[1], Monopolis, I.[1], Dekker, N.[3], Aerts, H.[3], Stefanis, L.[2,4] and Michelakakis, H.[1]

[1]Department of Enzymology and Cellular Function, Institute of Child Health, Athens, Greece
[2]Division of Basic Neurosciences, Biomedical Research Foundation of the Academy of Athens, Athens, Greece
[3]Department of Medical Biochemistry, Academic Medical Center, Amsterdam, The Netherlands
[4]Second Department of Neurology, National and Kapodistrian University of Athens Medical School, Athens, Greece

Increased dimerization of α-synuclein was recently reported in erythrocyte cell membranes from Gaucher disease (GD) patients. We further investigated this phenomenon in relation to lipid abnormalities and oxidative stress previously described in GD.

Overall 27 GD patients and 13 age matched controls were studied. In addition to the previously reported α-synuclein, plasmalogens, glucosylceramide and MDA levels, long chain saturated and unsaturated fatty acids were also determined, using GC, in erythrocyte cell membranes.

Statistically significant differences between GD patients and controls were observed in C16:0, C18:0, C20:0, C18:1ω9, C18:1ω7, C18:2ω6, C20:2ω6 (increased in GD) and C22:4ω6, C22:5ω6 (decreased in GD).

In GD patients the α-synuclein dimer/monomer ratio showed a significant negative correlation to MDA levels and the C16:0 plasmalogen species, whereas a significant positive correlation was observed with glucosylceramide, the glucosylceramide/ceramide ratio and C20:0.

Our results indicate that the increased dimerization of α-synuclein observed in erythrocyte cell membrane fractions correlate to lipid abnormalities and the increased oxidative stress observed in Gaucher disease patients.

P-22

α-SYNUCLEIN rs356219 POLYMORPHISMS IN PATIENTS WITH GAUCHER DISEASE AND PARKINSON DISEASE

Ioscovich, D.[1], Altarescu, G.[2], Alcalay, R.N.[3], Zimran, A[1], Elstein, D[1]

Gaucher Clinic[1] and Genetics Unit[2], Shaare Zedek Medical Center, affliated with the Hadassah-Hebrew University Medical School, Jerusalem, Israel; and the Department of Neurology and the Taub Institute[3], Columbia University Medical Center, New York, NY, USA

Objective: Mutations in β-glucocerebrosidase, the genetic defect in Gaucher disease (GD), are an important susceptibility factor for Parkinson disease (PD). A PD effector is α-synuclein (*SNCA*) hypothesized to selectively interact with β-glucocerebrosidase under lysosomal conditions. *SNCA* polymorphism rs356219 may be associated with early-age-onset PD, common among patients with GD+PD. The objective of this study was to ascertain rs356219 polymorphic genotypes of GD+PD patients.

Method: All GD+PD patients at our Gaucher clinic were invited. A GD-only sex-, age-, GD genotype-, and enzyme therapy (ERT)-matched control was found for each GD+PD participant. Student's t-test was used (p-value of <5% as significant).

Results: There were 14 GD+PD patients: all Ashkenazi Jewish; males=11(78.6%); mean (range) age diagnosed GD=34.2 (5-62) years; 50% N370S homozygous; mild to moderate GD; 3 asplenic and only these have osteonecrosis; 5 received ERT; mean age (range) diagnosed PD = 57.8 (43-70) years; first PD sign=tremor in 9 (64.3%); cognitive dysfunction in all. In GD+PD, frequency for AG+GG genotype (9) was greater than AA (5); in GD only, there was equality (7). Odds Ratio risk for PD increases with number minor alleles: here this was not significantly greater among GD+PD than GD only; in aggregate, there was no difference between cohorts for frequency of minor polymorphisms. The limitation of this study is few GD+PD, albeit virtually the entire GD+PD cohort among >500 adult GD patients in our clinic.

Conclusion: As a foray into potential genetic GD susceptibility for a synucleinopathy, this study suggests the need for collaboration to achieve larger numbers.

P-23

GBA 1 AND 2, FACTORS TO CONSIDER IN PARKINSON'S DISEASE?

Burke, D.†, Vellodi, A., and Heales, S.

Department of Chemical Pathology, Great Ormond Street Hospital & UCL Institute of Child Health, London †Email derek.burke@gosh.nhs.uk

It is now apparent that there is an increased risk of developing Parkinson disease (PD) in both Gaucher disease (GD) patients and heterozygotes. The exact mechanism for this increased risk is still unknown. Recently, we demonstrated that non lysosomal GBA2 is elevated in a GD mouse model and in some GD patients. Currently, it is not known; (a) what the relative contributions of these enzymes are to the GD/PD story and (b) how these two enzymes interact. Here we have examined the effects of GBA1 inhibition of GBA2 activity and vice versa.

Methods
SHSY5Y cells were incubated with either a GBA1 (CBE) or GBA2 (NBDNJ) inhibitor for 6 or 17 days.

Results
After 17, but not 6, days GBA1 inhibition there was a small (30%) but significant increase in GBA2 activity. Following 17 days GBA2 inhibition, GBA1was increased but not significantly. When compared to 6 days, GBA1 activity was significantly decreased by 17%. Under all conditions there were no significant effects on control enzymes (b-galactosidase, total b-hexosaminidase).

Conclusions
Our preliminary data may indicate that neuronal GBA1 deficiency can trigger an increase in GBA2 activity. Loss of GBA1 activity over 6 – 17 days in culture could point to a particular vulnerability of this enzyme. Whether brain ageing leads to a similar phenomenon remains to be demonstrated.

P-24

STUDY OF THE DISTRIBUTION OF DERIVATIVES OF L-IDONOJIRIMYCIN IN NERVOUS TISSUES

Alfonso, P.[1,2,3†], Gervas, J.[2,3], Andreu, V.[2,3], García-Moreno, I.[4], Mari-Beffa, M.M.[5], Urdiales Ruiz, J.L.[1,6], Sánchez-Jiménez, F.[1,6], Ortiz-Mellet, C.[4], García-Fernández, J.M.[7], Giraldo, P.[1,2,3,8]

[1]Biomedical Network Research Center on Rare Diseases (CIBERER), ISCIII, Valencia, Spain; [2]Traslational Research Unit, Miguel Servet University Hospital, Zaragoza, Spain; [3]Aragon Institute for Health Sciences of Aragon (IACS), Zaragoza, Spain; [4]Department of Organic Chemistry, Faculty of Chemistry. University of Sevilla, Spain; [5]Department of Celular Biology and Genetics, University of Málaga, Spain; [6]Department of Molecular Biology and Biochemistry, University of Málaga, Spain; [7]Institute for Chemical Research (IIQ), CSIC-University of Sevilla, Spain; [8]Hematology Department, Miguel Servet University Hospital; Zaragoza, Spain †e-mail: mpalfonso.iacs@aragon.es

Enzyme Replacement Therapy for Gaucher Disease (GD) has proved successful mainly for visceral and hematological symptoms. However, since the recombinant enzyme does not cross the blood–brain barrier (BBB), its efficacy for the disease types with neurological involvement is limited.

Therapeutic strategies for types 2 and 3 GD include the development of pharmacological chaperones capable of promoting the correct folding and trafficking of mutant glucocerebrosidase (GCase). The L444P mutation represents a particularly challengue since it is located far from active site, where chaperones generally bind.

Previously we evaluated the effect of three bicyclic derivatives of L-idonojirimycin-related sp^2-iminosugars on the residual GCase activity in fibroblasts derived from homozygous L444P GD patients. The preliminary results showed an increase of the residual enzyme activity by 1.5-3.0-fold.

In order to evaluate their potential to cross the BBB, we have studied the distribution of a dansyl-labelled analogue in nervous tissues using zebrafish model.

First, the L444P fibroblast cell line was treated with the fluorescent chaperone and grown in medium with Lysotracker Red DNS-99. Fluorescent images showed colocalization with lysosomal marker. Next, zebrafish embryos were developed for 10 days to form the BBB and then exposed to the fluorescent molecule, added in the water medium, at different concentrations. Preliminary results evidenced localization of the chaperone in rich structures in neurons and glia.

Conclusion: Apart from the enhancement of residual GCase activities in homozygous L444P GD cells, the new results suggest that L-idonojirimycin-type chaperones are capable to reach the nervous system in the zebrafish model.

Acknowledgement: This work was supported by the Institute of Health Carlos III (ISCIII) (contract number PI12/01219).

P-25

BRAIN-DERIVED NEUROTROPHIC FACTOR INCREASES AFTER ENZYME REPLACEMENT THERAPY IN GAUCHER DISEASE

Vairo, F.[1,2,3], Sperb-Ludwig, F.[2,3], Wilke, M.[1], Michellin-Tirelli, K.[1], Burin, M.[1], Netto, C.[1], Neto, E.C.[4], Schwartz, I.[1,3,5]

[1]Medical Genetics Service, Hospital de Clinicas de Porto Alegre, Brazil
[2]Post Graduation Program of Genetics and Molecular Biology, Universidade Federal do Rio Grande do Sul, Brazil
[3]BRAIN Laboratory, Hospital de Clínicas de Porto Alegre, Brazil
[4]CTN - Centro de Triagem Neonatal, Porto Alegre, Brazil
[5]Department of Genetics, Universidade Federal do Rio Grande do Sul, Brazil

Mutations on *GBA* gene has been related to increase the risk of development of neurodegenerative diseases. The exact molecular mechanisms involved in the interaction between *GBA* and α-synuclein, the main agent in some of these neurological diseases, remain unsolved. Brain-derived neurotrophic factor (BDNF) is a neurotrophin that is important for the normal development of the peripheral and central nervous system and play a key role in neuronal survival and synaptic plasticity in the adult brain. A reduction of BDNF expression has been reported in patients with Parkinson's disease, Alzheimer's disease and dementia with Lewy bodies. We analyzed BDNF levels in plasma of GD patients off ERT and after ERT and compared with healthy volunteers. We demonstrated that BDNF levels are remarkably diminished in GD patients with no specific treatment and after 6 months of ERT the levels increased more than 3 times. This is the first study that demonstrates a variation in plasma levels of neurotrophic factor in GD type 1 patients. More extended studies are required to relate BDNF level variations to clinical findings and response to therapy in GD patients. Since low levels of BDNF are related to neurodegenerative diseases, it could be a new therapeutic target for GD patients with neurological symptoms.

P-26

CORRELATION BETWEEN BRAIN MR SPECTROSCOPY AND BMB SCORE IN TYPE 1 GAUCHER'S DISEASE: IS THERE ANY?

Bertholdo, D.[1,2], Vairo, F.[3,4,5], Vanz, A.P.[3], Vedolin, L.[6,7], Schwartz, I.[3,5,8]

[1]Clínica Diagnóstico Avançado por Imagem (DAPI), Curitiba, Brazil
[2]Radiology Unit. Hospital de Clínicas da Universidade Federal do Paraná, Brazil
[3]Medical Genetics Service, Hospital de Clinicas de Porto Alegre, Brazil
[4]Post Graduation Program of Genetics and Molecular Biology, Universidade Federal do Rio Grande do Sul, Brazil
[5]BRAIN Laboratory, Hospital de Clínicas de Porto Alegre, Brazil
[6]Radiology Service, Hospital de Clínicas de Porto Alegre, Brazil
[7]Department of Internal Medicine and Post Graduation Program on Medical Sciences:Medicine, Universidade Federal do Rio Grande do Sul, Brazil
[8]Department of Genetics, Universidade Federal do Rio Grande do Sul, Brazil

Type 1 Gaucher's Disease (GD) is the non-neuronopathic form, with bone and visceral abnormalities being its main clinical findings. Some authors, however, have found neurological involvement in type 1 GD. Proton Magnetic Resonance Spectroscopy (^{1}H-MRS) is a diagnostic non-invasive imaging tool to detect and quantify different metabolites. In neuronopathic forms of GD (types 2 and 3), brain ^{1}H-MRS has shown lipid peak and higher choline/creatine ratios. For non-neuropathic form of GD, ^{1}H-MRS has also depicted higher Cho/Cr ratios. Magnetic Resonance Imaging (MRI) is a semiquantitative method to evaluate bone marrow infiltration. Different scores may evaluate the severity of bone involvement in GD, and the most used is bone marrow burden score (BMB). The aim of our study is to correlate ^{1}H-MRS brain metabolites to severity of bone marrow involvement using BMB score. Thirteen patients type 1 GD (mean age of 28 years), were submitted to brain, lumbar spine and femur MRI. ^{1}H-MRS was performed on basal and Cho/Cr, N-acetyl-aspartate/Cr and NAA/Cho ratios were calculated. Lumbar spine and femur MRI was performed at the same day and BMB score was calculated. ^{1}H-MRS metabolite ratios were compared to BMB score. BMB average score was 8. There was a low positive correlation between BMB score and Cho/Cr (r=0,19; P=0,001) and Cho/NAA (r=0,21; P=0,001) ratios and a low negative correlation between BMB score and NAA/Cr (r=-0,17; P=0,001). In conclusion, higher Cho/Cr and Cho/NAA ratios and lower NAA/Cr in brain ^{1}H-MRS correlate to a more severe bone marrow involvement in type 1 GD. Support: Genzyme/Actelion.

P-27

GAUCHER DISEASE TYPE 3A TREATMENT WITH TALIGLUCERASE

Cravo, R.[1], Jardim, E.[1], Rotman, V.[2], Guimarães de Noronha, T.[2], de Sousa Maia, M.de L.[2]

[1] State Hematology Institute Arthur de Siqueira Cavalcanti, Rio de Janeiro, Brazil
[2] Immunobiological Technology Institute Bio-Manguinhos, Rio de Janeiro, Brazil
†Presenting author: Renata Cravo, MD; Gaucher Disease Ambulatory Supervisor; email: renata.cravo@hemorio.rj.gov.br

Gaucher disease (GD) type 3 has an estimated incidence of 1 in 200,000, is pan ethnic, with clusters in Northern Europe, Egypt and East Asia. It is classified in three types according to clinical presentation. Type 3a is characterized by mild-to-moderate hepatosplenomegaly and slowly progressive neurologic deterioration. As recombinant enzyme does not cross the blood brain barrier, its use for type 3a is controversial. However, other somatic symptoms may respond to ERT and neurologic disease can be stabilized. We are going to describe a type 3a patient with L444P+A456P/G377S mutation, whose diagnosis was made in 2004, when he was 4 years old and started to have seizures. He was initially treated with imiglucerase at a dose of 60 U/Kg, every two weeks, progressive increased to 120 U/Kg, when neurologic stabilization was achieved. In 2009, there was a progressive reduction in the delivery of imiglucerase to Brazil, with interruption in 2010, when Brazilian Ministry of Health and the local sanitary agency decided to offer taliglucerase for all the patients who agreed. In this context, and as the patient was presenting neurologic deterioration, he was treated with 120 U/Kg of taliglucerase every two weeks, adjusted progressively to 30 U/Kg weekly, after expert consensus. After 2 years of taliglucerase, medium values of laboratory indexes were similar to values during imiglucerase therapy, as where ultrasonography measures and magnetic ressonance evaluations. Seizures where stabilized and no new bone lesion was detected. In this clinical case of GD 3a, treatment with taliglucerase was effective without severe adverse events.

P-28

FATIGUE SCORE GAUCHER DISEASE (FSGD): A NEW TOOL TO ASSESS FATIGUE IN TYPE I GAUCHER DISEASE

Reinke, J., Krause, J., Mengel, E.

Villa Metabolica, University Medical Centre Mainz, Germany

Gaucher disease, an autosomal recessive lysosomal storage disease caused by deficiency of the enzyme glucocerebrosidase, is a highly heterogenous multisystemic disease.
The disease is classified into three subtypes based by the absence (Type I) or the presence (type II and III) of neurological manifestations.
Clinical manifestations in type I Gaucher disease includes hepatosplenomegaly, thrombocytopenia, bone disease, bleeding diathesis and fatigue.
But in contrast to viszeral and hematological symptoms, pathophysiology and clinical manifestation of fatigue is poorly understood.
According to our experience particularly during shortage of enzyme therapy, fatigue is one of the most serious symptoms interfering with the activities of daily living and thereby influencing quality of life.
The objective of this study was to develop and validate a new tool, the “Fatigue Scale Gaucher Disease(FSGD)”, for the assessment of Gaucher-related cognitive and motor fatigue.
A total of 55 adult Gaucher patients (type I) and 85 healthy controls will be included in this study.
The first analysis showed that fatigue is in more than half of the patients, one of the leading clinical symptoms. The item-analysis and validation procedure of FSGD provided first indications of a high sensitivity and specifity in detecting fatigue in Gaucher disease.
Further investigations are intended to show the connection with severity of hematological, vizeral and in particular bone manifestation.
In conclusion, the FSGD will be a promising new tool to investigate pathophysiology of Gaucher disease.

P-29

RETHINKING FATIGUE IN GAUCHER DISEASE

Chen Zion, Y.[1], Pappadopulos, E.[2], Wajnrajch, M.[2], Sandberg, D.E.[3], Rosenbaum, H.[1]

[1]Rambam Medical Center, Haifa, Israel, [2]Pfizer, New York, NY, USA, [3]University of Michigan Medical School and C.S. Mott Children's Hospital, Ann Arbor, MI, USA

Gaucher disease (GD) is a rare, lysosomal storage disorder caused by functional defects in the enzyme acid β-glucosidase. Along with hematologic and visceral symptoms of GD, patients can experience chronic fatigue resulting in functional disability and reduced quality of life. Although patients with GD consider fatigue a core symptom, few clinical studies have systematically assessed it. The absence of practice guidelines regarding the measurement of fatigue in GD may discourage health care providers from measuring this domain. This significant gap is reflected in the scientific literature; a MEDLINE search of “Gaucher disease” AND “fatigue” generated minimal results (MeSH terms, n=4; text terms, n=14). Of these studies, one showed that patients with GD considered fatigue one of the most debilitating symptoms of the disease, negatively impacting the ability to perform school, work, and social activities. The Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) is a short, 13-item, tool that measures a patient’s level of fatigue during daily activities over the past week. FACIT-F has demonstrated equivalence in interview vs self-report formats, can be used in clinical settings, and has been translated in >45 languages. The modified Fatigue Severity Scale (mFSS) is a 9-item, self-report questionnaire that rates fatigue severity on a scale of 0 to 10, and has been highly correlated with the FACIT-F. Finally, the National Institutes of Health Patient Reported Outcomes Measurement Information System (PROMIS) Fatigue Short Form is a 7-item, patient self-assessment of fatigue severity on a scale of 1 (not at all) to 5 (very much). These symptom-specific scales have been used to assess fatigue severity in numerous chronic illnesses (eg, depression, cancer, rheumatoid arthritis, stroke), but generally not in GD. Evidence of FACIT-F sensitivity to treatment effects in GD comes from a recent study reporting significant improvements in fatigue following weekly acupuncture sessions. The effects of approved enzyme replacement therapies (ERTs), imiglucerase, velaglucerase alfa, or taliglucerase alfa, on GD-related fatigue has yet to be determined. A limited number of early studies reported improvements in fatigue symptoms following ERT, although no fatigue-specific scales were used. We plan to draw upon the literature discussed above to inform the development of a culturally sensitive measure of fatigue that is not linked to literacy. The goals of this presentation are to: 1) establish the need for reliable, validated, and highly specific tools for assessing fatigue in clinical trials and the clinical treatment of GD; 2) set forth an approach to develop such a measure; and 3) propose an expert consensus project to establish the criteria for clinically significant fatigue in GD.

P-30

SKELETAL MANIFESTATIONS IN GAUCHER DISEASE, MORE THAN BONE CRISIS

Andrade-Campos, M.[1,2,3,4†], Roca, M.[5,6], Giraldo, P.[1,2,3,6]

[1]Haematology Department, Miguel Servet University Hospital, Zaragoza; [2]CIBER de Enfermedades Raras (CIBERER); [3]Aragon Institute of Health Sciences (IACS), Zaragoza, Spain. [4]Rio Hortega Researcher; [5]International Skeletal Society-Radiodiagnostic Center; [6]Spanish Foundation for the Study and Therapy of Gaucher Disease and other Lysosomal Disorders (FEETEG)

†Presenting author: Marcio Andrade-Campos, Traslational Research Unit, Miguel Servet University Hospital; Paseo Isabel La Catolica 1-3. Zaragoza, Spain 50009; mandrade@salud.aragon.es

Gaucher disease (GD), the most prevalent lysosomal storage disorder is characterized by multisystem involvement; skeletal disturbances, one of the most frequent manifestations are caused by several factors: derived cell accumulation, associated with vascular events and cytokine release. MRI has demonstrated to be the gold standard for assesses bone involvement; the classical or typical bone manifestations include: infiltration, bone crisis and avascular necrosis; others like vertebral collapses secondary to infiltration-osteopenia and osteoporosis are common too; however there are other atypical findings registered during the follow-up of GD patients.

Of the 372 patients included in the Spanish registry of GD (www.feeteg.org) 126 patients (naïve and under therapy) have been evaluated by MRI (same radiologist and same MRI unit), in the Reference Unit of GD and other LSD. Here we present the analysis of these atypical MRI findings.

Results: 73 (58%) patients show aberrations in the MRI exam, outside typical alterations, we found atypical lesions: osteomyelitis 3; hemangiomas 5; syringomelia 1; spondilodiscitis 1; bone metastasis 2; degenerative discopathy 15 patients; neuropathic arthropathy-like of the knee and shoulder 7; unconfirmed Gaucheroma of the knee 1, muscle GD-infiltration 1; Perthe's deformity 1, multiple myeloma infiltration 1 and intraoseum lypoma: 1 patient.

Despite the typical MRI-lesions there were many findings registered in GD patients. It's difficult to say if GD predispose to others manifestations like the degenerative discopathy and neuropathic arthropathy-like, but is clear that with the actual management of the disease the reference units have to be prepared to offer an integral assessment of the skeletal manifestation.

P-31

HEALTH-RELATED QUALITY OF LIFE OF IN PATIENTS WITH GAUCHER DISEASE AND HIP OSTEONECROSIS

Mansano, L., Bregman, A., Elstein, D.*, Zimran, A.*, Lebel, E.

Department of Orthopedic Surgery and *Gaucher Clinic, Shaare Zedek Medical Center, Jerusalem Israel

Background: Since the advent of enzyme replacement therapy (ERT) for Gaucher disease patients' quality of life has improved substantially, but the response of bones lags behind that of the viscera. Osteonecrosis leading to joint arthrosis is irreversible, and remains a substantial cause of disability and reduction in quality of life (QoL). Total hip replacement (THR) in both young (<40 years of age) and older patients receiving ERT showed excellent results with relatively few complications, high patient satisfaction and improved function. Nevertheless, timing of THR and patient-reported satisfaction has not been previously assessed.

Patients & methods: All Gaucher patients known to have hip arthrosis or those having THR followed in our clinic were included. QoL was assessed by a validated self-reporting questionnaires (SF-36 and EuroQol [EQ-5D™]), a clinical tool (Harris Hip Score; HHS) and by open-ended queries in Gaucher patients with ≥1 year post-THR and Gaucher patients with hip arthrosis. IRB approval was received.

Results: Of 17 hip arthrosis patients, 7 patients (41.2%) were included (5 females; mean age: 49.6 years with range 39-63 years). Of 38 THR patients, 18 patients (47.4%) were included (9 females; mean age: 58.7 years with range 31-76 years). Mean Physical Component Summary of the SF-36 questionnaire showed a significantly higher score in the THR group (44.21) in comparison to the hip arthrosis group (32.95). The mean Mental Component Summary showed similar differences (54.1 versus 48.2, respectively). The EQ-5D results also showed significantly higher mean scores for the THR group relative to the hip arthrosis group (0.81 versus 0.66 respectively) as well as the VAS score (75/3 and 67/1, respectively). HHS scores were lower in the hip arthrosis group (mean 71 points) and higher in the THR group (mean 77 points). Two cardinal questions in the open-ended query (did THR improved your QoL? and would you recommend THR?) were answered very positively by the THR group.

Discussion: Self-reported questionnaires reflect significantly higher QoL after THR in patients with Gaucher disease suffering from hip arthrosis. Clinical assessment showed non-significant differences. Open ended questions added the patients' impression that surgical intervention should have been suggested earlier.

Conclusions: This is the first study, reporting improvement of self-reported quality of life of patients with Gaucher disease after hip arthroplasty. This intervention should be discussed with patients sustaining femoral head osteonecrosis.

P-32

LONGEVITY OF HIP ARTHROPLASTY IN PATIENTS WITH GAUCHER DISEASE

Abu-Dalu, K., Elstein, D., Zimran, A., Peyser, A., Lebel, E.

Department of Orthopedic-Surgery and Gaucher-Clinic, Shaare Zedek Medical Center, Jerusalem, Israel

Background: Total hip arthroplasty (THA) for young patients presents unique challenges due to increased demand for physical functionality and consequently the need for greater resistance to implant wear and loosening. Gaucher disease patients may suffer femoral head osteonecrosis in early adulthood and hence may require THA at very young age. Metal-on-metal (MoM) bearing THAs appeared appropriate since very low wear rates were reported. Recently, high failure rates were noted specifically for this type of implant. Herein we present our experience with MoM implants relative to other cementless hip arthroplasty implants in patients with Gaucher disease.

Patients and methods: Since 1992, 35 cement-less THAs for 32 patients with Gaucher disease were performed. Six THAs were MoM bearings for young, active patients. These implants were selected due to claimed low-wear and higher expected longevity. The remainder was metal on polyethylene (MoP) or ceramic on ceramic (CoC) bearing-surface implants.

Results: Study included 16 females (50%) and 16 males; mean age at surgery was 44 (range 31-85) years; implants' bearing surfaces included 18 MoP, 11 CoC, and 6 MoM. All patients having MoM implants reported pain and 2 have already undergone revision (after 5 and 16 years). Of the MoP implants, 6 (33%) had pain and required revision, occurring after relatively long follow-up period (mean 13, range 5-27 years). None of the patients with CoC had pain or require revision**.**

Discussion and conclusion: Cement-less hip arthroplasty leads to pain relief and functional improvement in patients with Gaucher disease and hip arthrosis. Longevity of hip implants was found to be good for CoC implants but less so for MoP. MoM implants did not provide long-term pain relief in any of the patients with these prostheses; probably due to wear debris accumulation about the prosthetic joint. This type of bearing-surface is recommended unless improved design and extended longevity will be reported.

P-33

BMP and Wnt SIGNALING INFLUENCES ON BONE HOMEOSTASIS IN TYPE I GAUCHER DISEASE

Zancan, I.[1], Bellesso, S.[2], Costa, R.[1], Salvalaio, M.[2], Filocamo, M.[3] and Moro, E.[1].

[1] Department of Molecular Medicine, University of Padova, Italy;
[2] Department Women's and Child's Health, University of Padova;
[3] Centro di diagnostica genetica e biochimica delle malattie metaboliche Istituto G. Gaslini, Genova, Italy

Bone mass is tightly controlled by the action of several developmental regulatory signals, which have important roles at various stages of osteoblast lineage cell development. Among key signaling pathways canonical Wnt and BMP signaling have been shown to regulate bone accrual during postnatal life, thus justifying the use of specific Wnt and BMP pathway modulators in bone-related disorders. Type I Gaucher disease (GD) patients are severely affected by osteopenia, osteonecrosis and bone pain, which are limitedly managed by the use of traditional enzymatic replacement therapy. Due to the lack of a complete understanding of GD–related bone pathogenesis, alternative pharmacological approaches are currently missing.

We performed a complementary approach based on the use of a biosensor fish and a fish model for type I GD to understand whether BMP signaling might be involved in glucocerebrosidase (Gba1) loss of function. We then made transcriptomic analysis on isolated fibroblasts from Gaucher patients and healthy donors to assess BMP targets expression levels.

We found that Gba1 functional impairment in fish triggers an increase in the BMP signaling activity, due to upregulation of key BMP transducers, such as Smad1 and Smad5. Higher Smad1 levels were consistently associated with downregulation of Wnt pathway activity. No apparent significant differences in sclerostin (SostT-1) expression levels were detected. Indeed, Type I Gaucher fibroblasts exhibited significantly higher SMAD1 expression levels.

Our results suggest that unbalanced Wnt and BMP activities precede bone defects in Type 1 GD, thus disclosing a new paradigm in type I GD bone pathogenesis.

P-34

ASSESSMENT OF BONE MARROW MICROVASCULAR NETWORK SUPPORTS THE CHRONIC INFLAMMATION CONCEPT IN UNTREATED GAUCHER DISEASE TYPE 1

Klimkowska, M.[1†], Palmblad, J.[2], Machaczka, M.[2]

[1]Department of Clinical Pathology and Cytology, Karolinska University Hospital Huddinge, Stockholm, Sweden; [2]Hematology Center Karolinska, Karolinska University Hospital Huddinge, Stockholm, Sweden

†Presenting author: Monika Klimkowska MD, PhD; e-mail: monika.klimkowska@karolinska.se

Background: Organ infiltration by glucocerebroside-laden macrophages is a hallmark of Gaucher disease (GD), leading to impaired organ function. Since monocytes/macrophages play a major role in chronic inflammation, it can be assumed that macrophage proliferation in GD can locally elicit inflammation-associated phenomena. The aim of the study was to analyze angiogenetic parameters in bone marrow biopsies (BMB) from untreated patients with GD type 1 (GD1), with respect to areas dominated by Gaucher cell (GC) infiltrates (>50% Gaucher cells) or containing mainly normal hematopoietic tissue (≤50% Gaucher cells).

Patients and methods: Study group consisted of 12 patients (3 F, 8 M), aged 21-86 years (median age 57 yrs). Ten patients carried at least one N370S allele; 4 patients were splenectomized. Bone marrow biopsies were immunohistochemically stained with anti-CD34 antibody. Following vessel parameters were assessed under high magnification using light microscope and image analysis software: total microvascular density (MVD) in BMB, MVD and vessel perimeters in GC-rich areas as compared to hematopoietic tissue.

Results: Median MVD counted randomly in 10 high power fields (HPF) containing microvascular hotspots was 10.2 (range 4.6-16.4). In GC predominated areas, MVD was higher than in hematopoietic tissue (median values 11 and 7.2, respectively) and so were average vessel perimeters (271.9 and 220.7 µm, respectively).

Discussion: Above mentioned preliminary results point to a more dense and complex microvascular pattern in areas of bone marrow tissue dominated by GC infiltrates. This finding supports the concept of chronic inflammatory response in organs infiltrated by Gaucher cells.

P-35

DELINEATION OF BONE CRISES IN THE SMALL BONES OF THE HANDS AND FEET IN PATIENTS WITH TYPE 1 GAUCHER DISEASE

Baris, H.N.[1†], Weisz Hubshman, M.[2], Kornreich, L.[3], Bar-Sever, Z.[4] and Cohen, I.J.[2]

[1] The Genetic Institute, Rambam Health Care Campus, Haifa, Israel;
[2] The Recanati Genetic Institute, Rabin Medical Center and Schneider Children's Medical Center of Israel, Petach Tikvah, Israel;
[3]Department of Radiology and [4]Department of Nuclear Medicine, Schneider Children's Medical Center of Israel, Petach Tikvah, Israel
†Presenting author: Hagit Baris Feldman, M.D.; Director of The Genetic Institute, Rambam Health Care Campus, Haifa, Israel; Phone: 972-4-8542456; Fax: 972-4-8543029; Email: hb_feldman@rambam.health.gov.il

The incidence of bone crises and fractures in Gaucher disease (GD) patients is reported. Bone events were divided into: Type 1 - bone crises of long bones (Type 1A - in atypical sites of bone crises such as pelvis). Type 2 - compression fractures of weight bearing bones (vertebrae, femoral head, calcaneus). Type 3 - "Romantic" fractures of ribs caused by over enthusiastic hugging in osteoporotic patients. Type 4 - crises in small bones of hands and feet. Of 100 type I GD patients, 30 (19 male, 11 female) (30%) experienced one or more bone crises. Only 2 had 3 Type 1A bone crises (pelvis). 90% had 1 or more type 1 bone crises. One or more Type 4 bone crises occurred in 43.3% patients and 33.3% had both Type 1 and 4. All Type 1 crises occurred before Type 4 crises. Eleven patients with 24 type 4 crises were found on MRI or bone scan and 2 had 3 clinically Type 4 crises. Eight patients had crises in one or both feet and three patients had crises in both hands and feet. Eighteen of the 30 (60%) patients with bone crises were N370S/84GG. Thirteen of the 15 splenectomised patients had documented bone crises (10 N370S/84GG genotype). Two of six women, mothers of children, suffered bone crises after childbirth. After treatment initiation, type 1 crises decreased and type 4 crises increased. Therefore, small bone crisis is a prevalent morbidity causing feature of GD with, as yet, no treatment.

P-36

A CASE OF SUCCESSFUL SURGICAL TREATMENT OF BONE COMPLICATIONS IN SPLENECTOMIZED CHILD WITH GAUCHER DISEASE TYPE 1

Gundobina, O.[1], Movsisyan, G.[1†], Namazova-Baranova, L.[1], Malahov, O.[1]

Gastroenterology departament, scientific center of children's health RAMS, Moscow, Russian Federation

†Presenting author: Goar Movsisyan, M.D.; Federal State Budgetary Institution; Russian Academy of Medical Sciences Scientific centre of Children health; 2 build.1, Lomonosovskiy prospect, Moscow, Russia; Mobile 8(929)5756061 E-mail: gongurik@mail.ru

Introduction: Skeletal involvement is a frequent sign in children with Gaucher disease (GD). Bone pathology in GD patients significantly reduces the quality of life, and often leads to disability. One of the main therapeutic goals is to prevent the development of irreversible skeletal pathology. In our days, when we have enzyme replacement therapy (ERT), using splenectomy for treatment is unacceptable, because this operation is a risk factor in the development of osteonecrosis of the femoral head. It is necessary as early as possible to diagnosis GD and start early ERT to prevent occurrence of skeletal complications and to determine a favorable prognosis. Unfortunately, in some cases, we have to apply surgical treatment ofbone complications. In this case we introduced the first successful experience of surgical treatment of bone complications in splenectomized child with GD in Russia.

Objective: to reportgood effects of surgical treatment of bone complications in splenectomized child with Gaucher disease type 1.

Case report: Female child at the age of eight years was hospitalized with pancytopenia, splenomegaly and hepatomegaly. Laboratory findings: moderate pancytopenia. Abdominal ultrasound: severe hepatosplenomegaly. Bone marrow biopsy identified Gaucher cells. Blood sample was taken to determine the activity of the lysosomal enzymes and revealed reduction of β-D-glucosidase - 1.6 mmol/lh (normal 4.7-19), and elevation of chitotriosidase activity to 14575 mmol/lh (normal 4.5-198), results consistent with GD.
In connection with severe splenomegaly child was splenectomized at the age of nine years. Examination after 6 years showed she had bone crises, pain, and stiffness in the left hip joint, gait disturbance with normal parameters of hemoglobin and thrombocytes. Computer Tomography (CT): signs of aseptic necrosis of the left femoral head and osteoporosis. The patient started to receive ERT in dose 60 U/kg every 2 weeks after only 1 year from the debut of skeletal symptoms. After one year of ERT we found improvements in height, weight, hepar volumes, bone crises and bone mineral density in the lumbar spine, however, limited mobility in the left femur joint and gait disturbance remained stable. Based on the results of CT she had deforming coxarthrosis of left hip joint and necessity for surgical treatment. The operation of total replacement of left femur joint made it possible to eliminate pain, fully restore the function of the operated leg and also provided higher social activity and quality of life to the patient.

Discussion: Splenectomy and a high interval between diagnosis and initiation of ERT associate with a high risk of severe skeletal complication of avascular necrosis in GD patients. In some cases we can successfully use surgical treatment of bone complications.

P-37

GAUCHER DISEASE AND BONE PROINFLAMMATORY PROFILE UNDER MIGLUSTAT THERAPY

Gervas-Arruga, J.[1,2,3,4†], Andrade, M.[1,2,3,4,5], Roca, M.[3,6], Giraldo, P.[1,2,3,4]

[1]Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER); [2]Translational Research Unit, Miguel Servet University Hospital, Zaragoza; [3]Spanish Gaucher Disease Foundation (FEETEG), Zaragoza, [4]IACS, Zaragoza; [5]Hematology Department, Miguel Servet University Hospital, Zaragoza; [6]International Skeletal Society-Radiodiagnostic Center, Spain

†Presenting author: Javier Gervás Arruga; Translational Research Unit, Miguel Servet University Hospital, Zaragoza, Spain; e-Mail: gervas.j@gmail.com

Introduction: Bone disease (BD) is one of the most debilitating and disabling complication of Gaucher disease (GD). Gaucher cells do not directly induce bone resorption but produce cytokines which enhance the osteoclastic activity that leads to bone destruction. BD in adult patients with GD improves more slowly with therapy although higher doses of ERT demonstrated improvements with respect to bone involvement. The information regarding SRT on BD is limited.

Aim: To analyze the cytokine profile in GD1 patients under SRT at long term.

Methods: A panel of cytokines: IL4, IL6, IL7, IL10, IL13, MIP1α, MIP1β and TNFα were analyzed in plasma samples from 49 GD1 patients at diagnosis and 71 healthy controls by Luminex®100 platform and Millipore cytokine kits. BD was evaluated by MRI and Ultra Sound Densitometry under the same conditions and observer in GD1 group. Plasma cytokines; Z-score; T-score and BUA were calculated at base line, 24, 48 and 72 months under SRT. Data were analyzed using non-parametric tests: Mann-Whitney-U, Kruskall-Wallis and the Spearman correlation.

Results: 14 GD1 under SRT complete the entire protocol (females 66%, mean age: 48,5 year; range: 25-75). We found significant differences (p<0.05) in IL4, MIP-1β, MIP-1α and TNFα values among controls; baseline GD1 and SRT. At 24 moths follow-up, BMD increase significantly (p<0.05) (Z-score and BUA rates). A significant positive correlation was found between MIP-1β and MIP-1α and significant negative correlations between MIP-1β; BUA and T-score.

Conclusions: These results suggest that SRT changes the pro inflammatory profile improving BMD in GD1 at long term therapy.

This work was partially financed by FIS and Fundación Española para el Estudio y Terapéutica de la Enfermedad de Gaucher (FEETEG) y otras lisosomales.

P-38

MONITORING BONE MARROW INVOLVEMENT IN GAUCHER DISEASE USING BONE MARROW BURDEN SCORE

Bertholdo, D., Vairo, F., Camargo, M., Vanz, A.P., Vedolin, L., Schwartz, I.

Universidade Federal do Rio Grande do Sul, Hospital de Clínicas de Porto Alegre, Brazil

Semiquantitative MRI is a useful tool to study bone marrow involvement and complications in Gaucher disease (GD). Bone marrow burden (BMB) score has been used to evaluate the severity and monitoring the bone involvement in GD patients. Our aim is to report the experience of the use of BMB score in the cohort of patients from the Reference Center for Gaucher Disease of Rio Grande do Sul State, Brazil.

Methods: Thirteen GD patients on treatment (12 GD type 1 and one GD type 3) were submitted to a lumbar spine and femur MRI at point 1 and at 12 months after (mean; point 2). BMB score was classified in four categories according to the severity: from 0 to 2 (no bone involvement), 3 to 7 (mild), 8 to 12 (moderate) and 13 to 16 (severe).

Results: Mean BMB score was 6.6 and 5.7, at points 1 and 2, respectively. At point 1, two patients had no bone involvement and 5 had mild bone disease, and there were no differences on the scores found at point 2. Three patients had moderate bone involvement; one of them had a significant decrease of BMB score at point 2 (from 12 points to 4 points). This patient started ERT one month before the basal MRI. Two patients had severe bone disease, and one of them had a decrease on BMB score on the follow up MRI (from 13 points to 10 points).

Conclusion: The use of BMB score is a useful tool to evaluate the bone marrow involvement in GD patients and their response to ERT. Our data suggest patients with a more severe bone marrow involvement have a faster response to ERT regarding the bone disease than patients with a mild bone marrow involvement.

Support: Genzyme, Actelion.

P-39

ASSESSMENT OF LIVER AND SPLEEN FIBROSIS IN PATIENTS WITH GAUCHER DISEASE USING FIBROSCAN

Rosenbaum, H.[1], Chen-Zion, Y.[1], Nimer, A.[2]

[1]Department of Hematology and Bone Marrow Transplantation Rambam Medical Center, Bruce Rappaport Faculty of Medicine, Technion, Haifa, [2]Liver disease service Ziv Medical Center, Bar Ilan University Safed, Israel.

Introduction : Hepatosplenomegaly in Gaucher disease (GD) is caused by infiltration of Gaucher cells, accumulation of glucocerebrosidase,infarcts and fibrosis. Irreversible hepatosplenomegaly is not infrequent in treated GD patients.

Goal: Assess liver and spleen stiffness and fibrosis using Fibroscan (EchoSens, Paris, France) in GD.

Methods: 26 GD patients were evaluated by transient elastography (TE) using Fibroscan.9 Naïve GD patients and 17 GD patients treated with enzyme replacement (ERT).Two cohorts of controls were investigated: healthy individuals and patients with nonalcoholic steatohepatitis (NASH).

Results: The liver TE measured in kpa showed increased fibrosis F4 with stiffness of 21.3 kpa and 17.4 kpa ,respectively, in two GD patients compatible with liver cirrhosis.In 4/26 GD patients mild to moderate fibrosis with stiffness range between 6.8 to 8.8 kpa was detected.The liver stiffness ranged between 1-6 kpa in healthy controls and between 7-9 kpa for moderate fibrosis(f2), 9-12 kpa for severe fibrosis (f3)and >12 for cirrhosis (f4) in patients with NASH.
The spleen stiffness in 3/26 was markedly increased to 75 kpa, in 10/26 the stiffness ranged between 25kpa - 36kpa indicating increased fibrosis.
Only 5/10 with spleen increased fibrosis were treated by ERT indicating a more severe course of GD and less responsive to ERT.
The increased spleen fibrosis correlated with splenomegaly only in two patients.The spleen stiffness ranged between 15-20 kpa in healthy controls. TE

Conclusion: Liver and spleen TE by Fibroscan might be used in GD patients with hepatosplenomegaly to evaluate fibrosis especially in resistant organomegaly in treated patients. Further clinical data will be reported regarding increased organ stiffness and the course of GD.

P-40

NEGATIVE ROLE OF SPLENECTOMY IN GAUCHER DISEASE: RUSSIAN EXPERIENCE

Lukina, K.[1], Sysoev,a E.[1], Yatsyk, G.[2], Mamonov, V.[3], Maksimov, A.[4], Lukina, E.[1]

[1]Department of Orphan Diseases, Hematology Research Center, Moscow, Russia; [2]Department of MRI and Ultrasound, Hematology Research Center, Moscow, Russia; [3]Department of Hematological Orthopedics, Hematology Research Center, Moscow, Russia; [4]Department of Radiology, Hematology Research Center, Moscow, Russia

Before the era of enzyme replacement therapy splenectomy has been the only treatment option for Gaucher disease (GD). Further clinical experience showed that splenectomy in patients with GD was associated with more severe disease, particularly in the skeleton.

Aim: to compare the severity of bone involvement in splenectomized and non-splenectomized patients with GD.

Methods and materials: the group included 100 treatment-naïve adult patients with GD type I aged from 16 to 79 years (median age 30 years): 36 males and 64 females. Splenectomy was performed in 39 patients in the past.
Standard radiographs and MRI of femurs, hip and knee joints were used to assess bone involvement.
The following criteria were used to characterize bone involvement:

– bone marrow infiltration;
– osteonecroses in diaphysis and/or metaphyses of femurs;
– avascular necroses of femoral heads;
– pathological fractures.

Results: patients were divided into 4 subgroups depending on the severity of bone involvement:

1. Mild – 14% patients,
2. Moderate – 58% patients,
3. Severe – 25% patients,
4. Extremely severe – 3% patients

Splenectomy was shown to be a strong risk factor for severe bone involvement ($p<0,0001$, OR=7,0 (CI 95% 2,6-18,4). The age of splenectomy was revealed to contribute: the mean age of splenectomy in patients with severe and extremely severe bone involvement was 11,6 years whereas in patients with mild and moderate bone involvement it was 19,6 years ($p=0,03$).

Conclusion: splenectomy is a risk factor for severe bone involvement in patients with GD. Hence splenectomy in Gaucher patients must be performed only in case special indications are present.

P-41

AN INTRIGUING CASE OF TYPE 1 GAUCHER DISEASE WITH UNCOMMON MANIFESTATIONS

Cassinerio, E.[(1)†], Poggiali, E.[(1) (2)], Casirati, G.[(1)], Nava, I.[(3)], Duca, L.[(3)], Baldini, I.M.[(1)], Soverini, G.[(1)], Cappellini, M.D.[(1) (2)]

[(1)] Rare Diseases Center, Department of Medicine and Medical Specialities, "Ca' Granda" Foundation IRCCS, Milan, Italy;
[(2)] Department of Clinical Science and Community Health, University of Milan, Milan, Italy;
[(3)] Department of Medicine and Medical Specialities, "Ca' Granda" Foundation IRCCS Ospedale Maggiore Policlinico, University of Milan, Italy
†Presenting author: Elena Cassinerio; Rare Diseases Center; Department of Medicine and Medical Specialities - Pad. Granelli-Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico; Via F. Sforza n.35, 20122 Milano - Italy-Tel +39 02/55033493; Fax +39 02/55033665 elena.cassinerio@virgilio.it

A 26-year-old man moving from Moldavia to Italy was referred to our Centre for type-1 Gaucher disease (GD). At the age of 5yrs "Langerhans cell histiocytosis" was diagnosed after splenectomy for massive splenomegaly, and treated with 3 cycles of CVPP without response. For recurrent severe bone crisis, GD was suspected and confirmed by undetectable beta-glucosidase activity at the age of 6yrs. He had a delayed puberal development treated with hormonal therapy since the age of 19yrs. At first admission to our clinic, the physical examination revealed eunuchoid appearance, markedly hypotrophic testicles, hepatomegaly and a systolic cardiac murmur. Abdominal US confirmed a severe hepatomegaly with increased stiffness. Echocardiography and cardiac MRI showed a severe left atrial enlargement. Blood tests revealed macrocytic anemia, thrombocytosis, leukocytosis, decreased B12 vitamin level and positive anti-PCA. Gastroscopy showed a chronic atrophic gastritis. The sexual hormonal profile confirmed the hypogonadotropic hypogonadism. Brain MRI, neurological examination and karyotyping were normal. Vitamin D deficiency was present. DEXA showed a severe osteoporosis. Massive bone marrow infiltration with Erlenmeyer flask deformities was documented by total body MRI. Few weeks after his arrival in Italy a pathological femural fracture occurred. The bone biopsy during surgery confirmed the diagnosis of GD, supported by markedly elevated chitotriosidase (35000 nmol/h/ml) and undetectable beta-glucosidase. Surprisingly, the GBA analysis identified only a single mutation (N370S). DNA analysis for uncommon mutations is ongoing. He is now on ERT (Cerezyme® 60 U/kg every two weeks). Are the hypogonadism, osteoporosis and autoimmune gastritis related to GD?

P-42

ANALYSIS OF INTESTINAL SACCHARIDASES PROFILE IN PATIENTS WITH GAUCHER DISEASE

Medrano-Engay, B.[1,2†], Irun, M.P.[3,4], Andreu, V.[1,2], Alfonso, P.[1,2,3], Bajador, E.[5], Pocovi, M.[3,4], Giraldo, P.[1,2,3]

[1]Traslational Research Unit. Hospital Universitario Miguel Servet. Zaragoza. Spain; [2]Aragon Health Sciences Institute (I+CS), Zaragoza, Spain; [3]Biomedical Network Research Center on Rare Biology and Diseases (CIBERER), ISCIII, Zaragoza, Spain [4]Department of Biochemistry and Cellular and Molecular Biology, University of Zaragoza, Spain [5]Department of Digestive, Hospital Universitario Miguel Servet, Zaragoza, Spain; †mbmedrano.iacs@aragon.es

Summary: Some inhibitors of substrate used in oral treatment of lysosomal storage diseases such as Gaucher disease (GD), are molecules derived of iminosugars. Miglustat reversibly inhibits, in a competitive way, intestinal disaccharidases that cleave α-glycosidically linked carbohydrates as sucrase, maltase and lactase. Disaccharides intolerance presents as malabsorption and symptoms like flatulence and diarrhoea.
Intestinal enzyme activity can be ascertained measuring gases on patient's breath. This is an alternative to define metabolic/functional disturbances.

Aims: To know disaccharidases activity profile in adult general population and in GD patients, and its influence on gastrointestinal side effects (GISE) in patients treated with Miglustat.

Methods: Prospective study of 20 healthy adults and 35 adult GD patients, selected from the Gaucher Disease Spanish Registry, aged 18-75.
Enzymatic disaccharidases activity was determined by specific commercial breath test; the analysis was performed centrally. www.isomed.com
Results were checked against genotyping using direct DNA sequencing.

Results:

	LACTOSE (%)		MALTOSE (%)		SACCHAROSE (%)	
GROUP	**Malabsortion**	**Intolerance**	**Malabsortion**	**Intolerance**	**Malabsortion**	**Intolerance**
CONTROL (20)	30	40	15	20	0	30
MIGLUSTAT (12)	33.3	16.7	16.7	25.0	8.3	8.3
NO MIGLUSTAT(20)	40.0	30.0	5.0	10.0	0.0	20.0

In group Miglustat: 3/12 (25%) present malabsortion to lactose, 1/12 (8%) to lactose and maltose, 1/12 (8%) to maltose and 1/12 (8%) to sacarose.
In group No Miglustat: 7/20 (35%) present malabsortion to lactose, 1/20 (5%) to lactose and maltose and 1/20 (5%) to sacarose

Conclusions: Disaccharides malabsorption in general population is high and similar to that observed in GD patients.
Symptoms of intolerance some disaccharide, appear in 55% of control subjects surveyed, in 4/12(33%) of the exposed to Miglustat and in amongst patients not exposed 8/20(40%).

P-43

TEN YEARS OF EXPERIENCE WITH MIGLUSTAT IN TREATMENT OF TYPE 1 GAUCHER DISEASE: THE SPANISH ZAGAL PROJECT

Giraldo, P.[1,2,21,23], Andrade, M.[1,2,21,23,24], Alfonso, P.[2,23], Irun, P.[2,22,23], Atutxa, K.[3], Acedo, A.[4], Barez, A.[5], Blanes, M.[6], Diaz-Morant, V.[7], Fernandez-Galán, M.A.[8], Franco, R.[9], Gil-Cortes, C.[10], Giner, V.[11], Ibañez, A.[12], Latre, P.[21], Loyola, I.[13], Luño, E.[14], Martin, E.[15], Puerta, J.[16], Roig, I.[17], de la Serna, J.[18], Salamero, O.[19], Villalon, L.[20] Pocovi, M.[2,21,22,23]

[1]Haematology Department, Miguel Servet University Hospital, Zaragoza; [2]CIBER de Enfermedades Raras (CIBERER); [3]Haematology Department, Basurto, Bilbao; [4]Haematology Department, Vega Baja Hospital. Alicante; [5]Haematology Department, Ntra Sra de Sonsoles Hospital, Avila; [6]Haematology Department, Virgen de la Salud Hospital, Elda; [7]Internal Medicine Department, Ronda Hospital, Ronda; [8]Haematology Department, Virgen del Puerto Plasencia, Plasencia; [9]Haematology Department, Punta Europa University Hospital, Cádiz; [10]Haematology Department, San Vicente Hospital. Alicante; [11]Internal Medicine Department, Virgen de Los Lirios Hospital, Alcoy; [12]Haematology Department. Complejo Hospitalario de Albacete; [13]Haematology Department, Complexo Hospitalario de Pontevedra; [14]Haematology Department, Central de Asturias University Hospital. Oviedo; [15]Haematology Department, Virgen de la Concha Hospital, Zamora; [16]Haematology Department, Virgen de las Nieves, Granada. [17]Haematology Department Parc Tauli Hospital, Sabadell; [18]Haematology Department, Doce de Octubre University Hospital. Madrid; [19]Haematology Department, Vall d'Hebron University Hospital. Barcelona; [20]Haematology Department, Alcorcon Hospital. Madrid; [21]Spanish Foundation for the Study and Therapy of Gaucher Disease (FEETEG); [22]Biochemistry and Molecular and Cellular Biology Department, Zaragoza University, Zaragoza; [23]Aragon Institute of Health Sciences (IACS), Zaragoza, Spain. [24]Rio Hortega Researcher

Real-world clinical experience with the substrate reduction therapy (SRT), miglustat (Zavesca®; Actelion Pharmaceuticals), in type 1 Gaucher disease (GD1) has developed in Spain since 2004. We report updated follow-up data from a prospective, open-label investigational study that evaluated miglustat 100 mg t.i.d. in the treatment of 63 patients with GD1 who were attending routine clinic visits; 20 naive patients and a further 43 patients who had been switched from previous enzyme replacement therapy (ERT). Long-term changes in organ size, blood counts, disease biomarkers, bone marrow infiltration, bone mineral density (BMD), and overall clinical status were analyzed. Safety and tolerability were also evaluated. Assessments were performed every 6 or 12 months. Approximately 69.8% of patients achieved and maintained therapeutic goals. The plasma biomarkers, chitotriosidase activity and CCL-18/PARC concentration, showed a trend toward progressive increases but did not show a good correlation with clinical activity. Bone marrow infiltration was reduced, as evidenced by a statistically significant decrease in S-MRI scores. Improvements in BMD were also observed after long-term monotherapy with miglustat. In safety and tolerability assessments, 39.6% of patients showed gastrointestinal disturbances and 38% discontinued miglustat therapy for this reason. Nevertheless, gastrointestinal adverse effects were reversible, and symptoms could be improved with a controlled diet or disaccharidase supplement. Also a reversible fine-hand tremor was developed in 60% of patients in the first month of therapy.

In conclusion, miglustat has been effective in the long-term maintenance therapy of treatment-naïve Spanish patients with mild or moderate GD1 and in patients previously stabilized with ERT.

P-44

ASSESSMENT OF GHRELIN, LEPTIN, ADIPONECTIN AND INSULIN LEVELS IN GAUCHER DISEASE TYPE I PATIENTS IN ENZYME REPLACEMENT THERAPY

Doneda, D.[(1)]; Lopes, A.L.[(2)]; Teixeira, B.C.[(2)]; Mittelstadt, S.D.[(3)]; Vairo, F.[(4)]; Schwartz, I.V. D.[(5,6)†]

[(1)] LTD Laboratory, Nutrition Program, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil;
[(2)] School of Physical Education, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil;
[(3)] Medical Student, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil;
[(4)] Medical Genetis Service, Hospital de Clínicas de Porto Alegre, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil;
[(5)] Genetics Department, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil;
[(6)] Post-Graduate Program in Medicine: Medical Science; Universidade Federal do Rio Grande do Sul (UFRGS), Brazil

†Author contact: Ida V.D. Schwartz; email: idadschwartz@gmail.com

Gaucher disease type I (GD-I) is characterized by clinical heterogeneity and symptomatic manifestations of varied intensity; energy homeostasis dysfunction is also present. **OBJECTIVE:** To assess ghrelin, leptin, adiponectin and insulin levels in patients with GD-I under enzyme replacement therapy (ERT).

METHODS: Controlled transversal study in GD-I patients, age over 18 yo and under ERT for at least 6 months (n=15); they were pair matched with healthy controls for sex, age and BMI.

RESULTS: Median of ghrelin and adiponectin levels of patients did not differ from that of the controls; leptin levels tend to be higher in the patients (p=0.05). Ghrelin and adiponectin levels presented positive correlation between themselves (ρ=0.580; p=0.024), with HDL-cholesterol (ghrelin: ρ=0.525; p=0.040; adiponectin: ρ=0.513; p=0.025), and inverse correlation with BMI (ghrelin: -0.587; p=0.022; adiponectin: ρ=-0.681; p=0.005), waist circumference (ghrelin: ρ=-0.511; p=0.045; adiponectin: ρ=-0.717; p=0.001), and triglycerides (ghrelin: ρ=-0.699; p=0.011; adiponectin: ρ=-0.593; p=0.010). Leptin levels presented inverse correlation with LDL-cholesterol (ρ=-0.459; p=0.042) and direct correlation with BMI (ρ=0.461; p=0.042), waist circumference (ρ=0.491; p=0.031), enzyme dose (ρ=0.491; p=0.031), triglycerides (ρ=0.581; p=0.023), insulin (ρ=0.832; p<0.001), and HOMA-IR (ρ=0.806; p<0.001). Eight patients met the criteria for metabolic syndrome, four of which had insulin resistance, as measured by the HOMA-IR index.

DISCUSSION/CONCLUSIONS: Leptin presented high association with insulin and with the HOMA-IR index, and may eventually become a biomarker to evaluate early evidence of insulin resistance in GD-I patients. Metabolic syndrome and insulin resistance seem to be frequent in GD-I patients. Further research is necessary to investigate the findings herein researched. SupportFIPE/HCPA

Keywords: Gaucher Disease – Ghrelin – Leptin – Adiponectin

P-45

CLINICAL RESPONSE TO ELIGLUSTAT IN TREATMENT-NAÏVE PATIENTS WITH GAUCHER DISEASE TYPE 1 (GD1): POST-HOC COMPARISON TO IMIGLUCERASE IN A REAL-WORLD SETTING

Mankoski, R.†, Taylor, J.S., Angell, J., Peterschmitt, M. J.

Genzyme, a Sanofi company, Cambridge, MA, USA

†Presenting author: Raymond Mankoski, M.D., Ph.D. Director, RARE Diseases, Global Medical Affairs, Genzyme, a Sanofi company; Telephone: 617-768-6006; Mobile: 857-253-8469; Fax: 617-768-6370; raymond.mankoski@genzyme.com

Objective: Compare long-term treatment response to eliglustat and imiglucerase in treatment-naïve GD1 patients.

Methods: Four-year data from eliglustat-treated patients in an open-label study (NCT00358150, N=26) and 9-month data from a randomized, double-blind, placebo-controlled study (ENGAGE: NCT00891202, n=20 in eliglustat arm) were compared to 75 matched imiglucerase-treated patients enrolled in the ICGG Gaucher Registry who had received at least 15 U/kg/2 weeks.

Results: At baseline, hematologic parameters were similar in the two groups but eliglustat patients had slightly larger spleens and livers. Time course and degree of improvement were similar for eliglustat and imiglucerase-treated patients for most parameters. After 4 years, mean spleen volume decreased by 63% and 48%, mean liver volume decreased by 27% and 30%, mean platelet count increased by 95% and 99%, and mean hemoglobin level (g/dL) increased by 2.27 and 0.71 in eliglustat and imiglucerase patients, respectively. Improvements in lumbar spine and femur z-scores were consistently higher in the eliglustat group at all time points; however, bone data were limited from the imiglucerase-treated patients. The z-score increases observed with eliglustat were higher than those observed by Wenstrup *et al.* (2007, J Bone Min Res) during low to high-dose treatment with imiglucerase (0.06–0.13 z-score/year) in patients who had similar mean baseline bone mineral density.

Conclusion: Although not a head-to-head trial, this post hoc analysis suggests that eliglustat, in treatment-naïve patients, results in improvements in organ volumes and hematologic parameters that are comparable to those observed with imiglucerase in a real-world setting.

P-46

ELECTROCARDIOGRAPHIC EVALUATION OF ELIGLUSTAT: RESULTS OF A THOROUGH QT STUDY AND PHASE 2 AND 3 STUDIES

Peterschmitt, M. J.[1†], Ruskin, J.N.[2], Ortemann-Renon, C.[1], Ross, L.[1], Mankoski, R.[1], Puga, A. C.[1], von Moltke, L.[1], Cox, G.F.[1]

[1]Genzyme, a Sanofi company, Cambridge, MA, USA; [2]Massachusetts General Hospital, Boston, MA, USA

†Presenting author: M. Judith Peterschmitt, MD Medical Director, Clinical Research; Genzyme, a Sanofi company; Phone: (617) 768-6663; Fax: (617) 768-9888; Email: Judith.Peterschmitt@genzyme.com

Introduction: Eliglustat, an oral substrate-reduction therapy being developed for adults with Gaucher disease type 1, inhibits glucosylceramide synthase thereby balancing substrate synthesis with impaired degradation. In vitro studies demonstrated that eliglustat inhibits human potassium, sodium, and calcium cardiac ion channels. We describe an electrocardiographic evaluation of eliglustat.

Methods: A thorough QT (TQT) study (NCT01659944) was performed with 47 healthy subjects in a randomized, double-blind, placebo- and positive-controlled (400 mg moxifloxacin) crossover study of single-dose eliglustat (200mg and 800mg; the latter supratherapeutic exposure exceeded maximum exposure at steady-state in patients receiving therapeutic doses). Additionally, patients were closely monitored for ECG changes during the Phase 2 and 3 studies.

Results: The TQT study was negative per ICH E14 guidance. In subjects receiving eliglustat, the largest time-matched mean QTcF differences versus placebo were 0.7msec (upper one-sided 95% CI of 3.5msec) and 6.5msec (upper one-sided 95% CI of 9.3msec) for the therapeutic and supratherapeutic doses, respectively. There was no apparent effect on heart rate, but concentration-related effects were observed on the QTcF, PR, and QRS intervals with predicted placebo-corrected changes from baseline at the mean geometric Cmax of the supratherapeutic dose of 5.7msec, 9.3msec, and 3.0msec, respectively. During ECG and Holter monitoring in Phase 2 and 3 studies, no patient experienced a QTcF >500msec or an episode of Mobitz II or higher degree heart block.

Discussion: Eliglustat had negligible effects on ECG parameters versus placebo in the TQT study. Modeling suggests that mild interval prolongations may occur at concentrations substantially above the therapeutic range.

P-47

LONG TERM EFFICACY AND SAFETY OF VELAGLUCERASE IN SIX PATIENTS WITH TYPE 1 GAUCHER DISEASE PREVIOSLY TREATED WITH IMIGLUCERASE

Ciana, G.[1†], Sechi, A.[1], Dardis, A.[1], Malini, E.[1], Zanin, I.[1], Romanello, M.[1], Brondani, G.[2], Cattarossi, S.[1], Macor, D.[1] and Bembi, B.[1]

[1] Regional Coordinator Centre for Rare Diseases, Academic Hospital "Santa Maria della Misericordia", Udine, Italy
[2] Department of Diagnostic Imaging, Emergency Radiology, Academic Hospital "Santa Maria della Misericordia", Udine, Italy

†Presenting Author: Giovanni Ciana, MD; Regional Coordinator Centre for Rare Diseases, Academic Hospital "Santa Maria della Misericordia", Udine, Italy; E mail: ciana.giovanni@aoud.sanita.fvg.it

Background: The temporary shortage in supply of imiglucerase in 2009-10 caused a forced drug dose reduction for patients with Gaucher disease type 1(GD1). In our casuistry, this was well tolerated in most of the patients, while few complained of asthenia and bone pain, 6 of them were switched to velaglucerase.

Patients and methods: Six GD1 patients, previously treated with imiglucerase, received velaglucerase beweekly at a dosage equal to that preceding the shortage (ranging from 60 to 120 U/Kg/month). Data on blood count, bone pain, energy, magnetic resonance abdominal and femoral imaging and lumbar spine DEXA scores were collected retrospectively from clinical records, from the time of the drug switch for up to 32 months.

Results: At the end of the follow up: all patients reported less asthenia, while bone pain improved in 3/6 patients. Haemoglobin increased more than 1.5 g/dl in one patient after 36 months, and remained stable (normal) in the other 5. Platelet decreased more than 15% from baseline in 2 previously splenectomized patients (who started with values > 300.000/mm3), possibly reflecting a reduction of the inflammation status, and remained stable in all the others. Liver and spleen volumes, bone imaging, and DEXA T scores did not change significantly. No side effects were reported.

Conclusions: Velaglucerase showed to be safe and able to maintain stable the main indicators of the disease burden.

P-48

SAFETY OF USE OF VELAGLUCERASE IN SIX PATIENTS WITH TYPE 1 GAUCHER DISEASE SHIFTED FROM IMIGLUCERASE

Ciana, G.†, Sechi, A., Dardis, A., Malini, E., Zanin, I., Romanello, M., Brondani, G., Cattarossi, S., Macor, D. and Bembi, B.

Regional Coordinator Centre for Rare Diseases, Academic Hospital "Santa Maria della Misericordia", Udine, Italy *Department of Diagnostic Imaging, Emergency Radiology, Academic Hospital "Santa Maria della Misericordia", Udine, Italy
Udine, Italy

†Presenting Author: Giovanni Ciana, MD; Regional Coordinator Centre for Rare Diseases, Academic Hospital "Santa Maria della Misericordia", Udine, Italy; E mail: ciana.giovanni@aoud.sanita.fvg.it

Background: The shortage of imiglucerase in years 2009-10 caused a reduction in supplying the drug to Gaucher type 1 patients. In our casuistry the reduction was well tolerated in most of the patients, while few suffered of this shortage with a symptomatology mainly dominated by asthenia and severe bone pain.

Patients and methods: In six of the latter patients, it was possible to shift from imiglucerase to velaglucerase, which was given at the dosage preceding the shortage (ranging from 60 to 120U/Kg/month). Four of these patients were splenectomised. Follow up was performed until 36 months of treatment

Results: After one years of follow up , an improvement of asthenia was documented in all the patients, bone pain improved in 3 patients .These clinical data remained stable during the next 2 years . Haemoglobin increased more than 1.5 g/dl in one patient after 36 months, while remained stable in the other 5 patients. Platelet decreased more than 15% from baseline in 2 patients, who started with values more than 320000/mm3. We hypothesized in this behaviour a reduction of global inflammation. Liver and spleen volume did not change significantly. MR of femurs did not show signification worsening of infiltration where present, while DEXA T score , measured al lumbar level, remained on the same values .Chitriosidase slowly showed to be globally decreased at the end of follow up .. No side effects were recorded

Conclusions: Velaglucerase (Vpriv) showed to be safe and able as imiglucerase in maintaining stable the main indicators of disease burden.

P-49

FOLLOW-UP OF ADULT PATIENTS WITH TYPE 1 GAUCHER DISEASE ON TALIGLUCERASE ALFA: A STUDY BASED ON BONE MAGNETIC RESONANCE

Mittelstadt, S.D., Vairo, F., Bertholdo, D., Schwartz, I.V.D.

Faculdade de Medicina and Departamento de Genética/UFRGS, Hospital de Clínicas de Porto Alegre, Rio Grande do Sul, Brazil

BACKGROUND: Alfataliglicerase was approved by the FDA in 2012 as an ERT option for patients with Gaucher disease (GD). In Brazil, this drug has been approved for prescription since 2011 due to the shortage of imiglucerase. The objective of this study is to evaluate the impact of taliglucerase alfa in the bone marrow infiltration (BMI) of adult type 1 Gaucher disease patients seen at a Reference Center from Southern Brazil, and who have been switched from imiglucerase to taliglucerase alfa.

METHODS: BMB scores from T1- and T2-weighted magnetic resonance images of the lumbar spine and femora were evaluated at the first (FYT) and the second (SYT) year of treatment with taliglucerase alfa (n= 5 patients).

RESULTS: At the time of the second resonance, the median patients' age was 46.1 yo (range: 26.9–59.5) and the median of treatment time was 11.9 years (range: 2.3–15.4). At switching, ERT dosage remained the same in three patients (two with 15 IU/kg/in and the other with 30 IU/kg/inf), was increased in one patient (15 IU/kg/inf to 30 IU/kg/in) and decreased in another one (45 IU/kg/inf to 30 IU/kg/inf). The median BMB score at FYT was 3 (range: 2-12) and remained stable at SYT for all patients. The higher scores were associated with less time of ERT.

CONCLUSIONS: This study suggests that the BMB score was sustained with taliglucerase alfa. Prospective studies in a large cohort of patients are needed to evaluate the real effect of the ERT with taliglucerase alfa in the BMI.

P-50

INITIAL RESPONSE TO ERT FOLLOWED BY WHOLE BODY MRI

Mengel, E., Moos, L., Reinke, J., Heidrich, A., Brixius-Huth, M., Staatz, G.

MC Johannes-Gutenberg-University Mainz, Department of Pediatric Radiology and the Villa Metabolica in the Center of Pediatric and Adolescence Medicine

Gaucher disease is a rare lysosomal disorder, which can be successfully treated with ERT since the nineteen`s. In Germany enzyme replacement therapy with recombinant glucocerbrosidase enzymes is standard. Initial therapy response was monitored with whole body MRI.

AIM: To show the initial response to ERT in type 1 patients treated with Imiglucerase or Velaglucerase within one year.

In this study of the Mainz cohort we include 5 new diagnosed patients treated with Cerezyme (3 patients), or VPRIV (2 patients). Age range 22- 51 years.. A whole body MRI was carried out by all patients at baseline and after one year during work-up routines. All whole body MRI`s were well tolerated from the patients. At baseline numerous pathological findings were detected which previously not be seen by sonography and x-ray. Especially wide outspread bone marrow infiltration as well as 2 – 5 AVN in all patients were seen. BMB und DGS decreased in all patients 1-3 points. Distal regions of the skeleton improved first. Liver and spleen volume decreased significantly. Blood count normalization was seen before normalization of viszeral normalization.

Whole body MRI gives an overview of bone marrow infiltration of the skeleton. More over typical and atypical Gaucher manifestation were diagnosed. Response to ERT regarding bone marrow infiltration and organ volume is visualizied und objectively measured. Both enzymes show effects in the same range, however the study give hints that age of initiating therapy may be important.

P-51

THE EUROPEAN GAUCHER ALLIANCE (EGA): A PROJECT TO TAKE FORWARD THE NEXT GENERATION OF LEADERS NATIONALLY AND INTERNATIONALLY

Lauridsen, A.-G.[1†], Cook, J.[1], Tomova, R.[1], Parkkinen, J.[1]

[1] European Gaucher Alliance, Evesham House Business Centre, 48 - 52 Silver Street, Dursley, Gloucestershire, GL11 4ND, UK

†Presenting author: Anne-Grethe Lauridsen; European Gaucher Alliance, Evesham House Business Centre, 48 - 52 Silver Street, Dursley, Gloucestershire, GL11 4ND, UK Email: anne-grethe@eurogaucher.org

Objectives: The EGA was established in 1994 and constituted in 2008 as an umbrella group supporting patient organisations for Gaucher disease (GD). This was the first event of its kind for the EGA and a pilot project to encourage young adult Gaucher patients to come together to exchange information and ideas and to help improve the quality of life of the participants, broaden their horizons and to also support the work of finding and strengthening the future leaders of the EGA and its member associations.

Methods: We sent a newsletter to all our members in May 2012 to advise them about the event and to ask them to nominate representatives. We also create a special website featuring information about the event and made a presentation at the EGA bi-annual meeting in Paris at end of June 2012.

The first 'Go with Gaucher' meeting took place in Frankfurt, Germany in November 2012 and was attended by thirty one young Gaucher patients, ranging in age from 17 to 34 years, representing twenty of our member countries. These included patients with both type 1 and type 3 Gaucher disease, mainly from Europe but Latin America and Africa were also represented.

Results: Feedback from the weekend has been used to shape some of the EGA's work programme for 2014 and future projects targeted at young Gaucher patients. A number of future potential leaders have been identified and many of these young patients have become more involved in the work of their national groups.

Conclusion: A number of future potential leaders have been identified and many of these young patients have become more involved in the work of their national groups.

P-52

THE EUROPEAN GAUCHER ALLIANCE (EGA): A SURVEY OF MEMBER PATIENT ORGANISATION'S ACTIVITIES, HEALTHCARE ENVIRONMENTS AND CONCERNS

Žnidar, I.[1†], Collin-Histed, T.[1], Niemeyer, P.[1], Parkkinen, J.[1], Lauridsen, A.-G.[1], Zariņa, S.[1], Cohen, Y.[1], Manuel, J.[1]

[1] European Gaucher Alliance, Evesham House Business Centre, 48 - 52 Silver Street, Dursley, Gloucestershire, GL11 4ND, UK

†Presenting Author: Irena Žnidar; European Gaucher Alliance, Evesham House Business Centre, 48 - 52 Silver Street, Dursley, Gloucestershire, GL11 4ND, UK; Email: Irena@eurogaucher.org

Objectives: The EGA was established in 1994 and constituted in 2008 as an umbrella group supporting patient organisations for Gaucher disease (GD). To develop its priorities and work programme, every two years the EGA conducts a questionnaire survey of member associations. Latest survey results are presented here.

Methods: Between June 2012 and April 2013, the EGA's 36 members and associate members were asked to complete a questionnaire detailing membership, patient's access to treatment, healthcare environment, organisation's activities and concerns. Questionnaires completed in 2012 were revised in January 2013; responses analysed between July and September 2013.

Results: Thirty three members returned data on one or more questions. Findings identified inequalities in treatment access within and between countries: 3/27 countries, for which data were available, relied totally on humanitarian aid for treatment and 6% of untreated patients in 20 countries were untreated because of funding issues. Access to treatment and reimbursement represented 45% of members' concerns, while 35% related to access to specialist treatment centres, home infusions and expertise in GD. Member associations' main activities centred on patient support (59% of responses) and raising awareness of GD and patients' needs (34%). Twenty one (78% of respondents) indicated they were the only source of help for GD patients in their country. Activities were often constrained by funds and maximised through collaborations; two members had no external funding source.

Conclusion: The survey provided a 'snapshot' of the situation for individuals affected by GD, helping the EGA direct its activities into areas of greatest need.

11th EWGGD, 2014 Haifa PARTICIPANTS LIST			
ABRAHAMOV	Ayala	Israel	abrahamova@szmc.org.il
AERTS	Johannes	the Netherlands	j.m.aerts@amc.uva.nl
AGNEW	Rebecca	Australia	ragnew@shire.com
ALEKSOVSKA	Vesna	Rep. of Macedonia	vesna.stojmirova@gmail.com
ALFONSO	Pilar	Spain	mpalfonso.iacs@aragon.es
ALMON	Einat	Israel	einata@protalix.com
ALTARESCUE	Gheona	Israel	gheona@szmc.org.il
ALVES PEDROSO	Maria Lucia	Brazil	malu.ap@uol.com.br
AMATO	Dominick	Canada	damato@mtsinai.on.ca
ANDRADE	Marcio	Spain	andradecampos@icloud.com
ARAULO MONTEIRO DE LIMA	Theresa Cristina	Brazil	theresa.lima@pfizer.com
ARBEL	Naama	Israel	naama@medison.co.il
ASH	Tammy	Canada	tash@shire.com
AVILA	Elsa	Mexico	elsa.avila@yahoo.com.mx
AZEVEDO	Simone	USA	simone.azevedo@genzyme.com
BABCHENKE	Liana	Israel	babchenko@gmail.com
BAGAL	Sukirti	USA	sukirti.bagal@pfizer.com
BARBOSA ALVES	Elisangela	Brazil	elisangela.b.alves@pfizer.com
BARBOUTH	Deborah	USA	dbarbouth@med.miami.edu
BARIS FELDMAN	Hagit	Israel	hb_feldman@rambam.health.gov.il
BELMATOUG	Nadia	France	nadia.belmatoug@bjn.aphp.fr
BETTMAN	Noam	Israel	noambett@rambam.health.gov.il
BIEGSTRAATEN	Marieke	the Netherlands	m.biegstraaten@amc.uva.nl
BINYAMINI	Noam	Israel	n_benyamini@rambam.health.gov.il
BISHARAT	Lina	Israel	l_bisharat@rambam.health.gov.il
BLIGNAUT	Liezl	South Africa	liezl@kidzhealth.co.za
BLUNK	Vivian	Brazil	vivian.blunk@pfizer.com
BOLDRINI	Arianna	Italy	arianna.boldrini@gmail.com
BONEH	Galya	Israel	galyab@medison.co.il
BOOT	Rolf	the Netherlands	r.g.boot@amc.uva.nl
BRAUNSTEIN	Hila	Israel	brown_hila@walla.com
BROWN	Dan	United Kingdom	dbrown@granthamproperties.co.uk
BUDRYTE	Diana	Lithuania	dianabudryt@gmail.com
BURKE	Derek	United Kingdom	derek.burke@gosh.nhs.uk
CABASSO	Or	Israel	orcaba@gmail.com
CAMOU	Fabrice	France	fabrice.camou@chu_bordeaux.fr
CASSINERIO	Elena	Italy	elena.cassinerio@virgilio.it
CHAVES	Rigarberto	Brazil	rigobertogadelha@hotmail.com
CHEN ZION	Yehudit	Israel	y_chen_zion@rambam.health.gov.il
CHERTKOFF	Raul	Brazil	raul@protalix.com
CHICCO	Gaya	Israel	gchicco@szmc.org.il
CHRONOPOULOU	Effie	United Kingdom	effie.chronopoulou@btinternet.com

11th EWGGD, 2014 Haifa PARTICIPANTS LIST			
CHURCH	Heather	United Kingdom	heather.church@cmft.nhs.uk
CIANA	Giovanni	Italy	ciana.giovanni@aoud.sanita.fvg.it
COHEN	Yossi	Israel	yossi7@bezeqint.net
COHEN	Ian Joseph	Israel	icohen@tau.ac.il
COLIN ARONOVICZ	Yves	France	yves.colin-aronovicz@inserm.fr
COLLIN	Madeline	United Kingdom	maddiecollin3@gmail.com
COLLIN-HISTED	Tanya	United Kingdom	tanya@eurogaucher.org
COOK	Joanne	United Kingdom	jo@eurogaucher.org
COOKE	Juniebel	United Kingdom	juniebel@nhs.net
COX	Timothy	United Kingdom	tmc12@medschl.cam.ac.uk
DAYAN	Galit	Israel	galitb@szmc.org.il
DE FATIMA AMARAL SOUTO GARGUR MARTINS	Maria	Brazil	fatimagrargur@gmail.com
DE LIMA GUEDES	Veronika	Brazil	veronikalima@ig.com.br
DEEGAN	Patrick	United Kingdom	patrick.deegan@addenbrookes.nhs.uk
DEGULYS	Andrius	Lithuania	andrius.degulys@santa.lt
DEUTSHER-CHERTKOW	Yael	Israel	y_deutsher@rambam.health.gov.il
DEZHENKOVA	Anna	Russia	dezhenkova@list.ru
DI ROCCO	Maja	Italy	majadirocco@ospedale-gaslini.ge.it
DIANA	Barbara	the Netherlands	barbara.diana@genzyme.com
DIAS ZANETTE	Angela Maria	Brazil	angela.zanetti@hotmail.com
DIMITROV	Kristiyan Plamenov	Bulgaria	pretty.cold@abv.bg
DINH	Quinn	USA	qdinh@shire.com
DINUR	Tama	Israel	dinurt@012.net.il
DOMB	Yael	Israel	yaeld@medison.co.il
DUBOKA	Davor	Serbia	davor.duboka@gmail.com
DURAN	Gloria	Chile	angelica.larrain@bcdtravel.cl
ĐURIĆ	Borislav	Bosnia & Herzegovina	rijetkebolesti.ba@gmail.com
ELSTEIN	Deborah	Israel	elstein@szmc.org.il
FADEL	Shiri	Israel	s_fadel@rambam.health.gov.il
FAGERSTROM	Annika	Sweden	annika.fagerstrom@travellink.com
FELDMAN	Ricardo	USA	rfeldman@umaryland.edu
FERNANDEZ FRANCO	Emiliano Rolando	Paraguay	sssla2010@gmail.com
FERNET	Mireille	Canada	mireille.fernet@pfizer.com
FERREIRA FERNANDES	Rachel Aparecida	Brazil	rachelhemato@gmail.com
FONESECA PORTO	Maria Aurelia	Brazil	mafporto@superig.com.br
FRANCO	Mélanie	France	melanie.franco@inserm.fr
FRANK	Cynthia	USA	cyndi@gaucherdisease.org
FREISENS	Selena	Germany	selena.freisens@genzyme.com
FUMIC	Ksenija	Croatia	ksenija.fumic@kbc-zagreb.hr
FUTERMAN	Tony	Israel	
GARCIA	Elias	Mexico	jose.elias.garcia@gmail.com
GASPAR	Paulo	the Netherlands	p.j.dasilvagaspar@amc.uva.nl

11th EWGGD, 2014 Haifa PARTICIPANTS LIST			
GERVAS ARRUGA	Javier	Spain	gervas.j@gmail.com
GIONA	Fiorina	Italy	giona@bce.uniroma1.it
GIRALDO	Pilar	Spain	giraldocastellano@gmail.com
GOKER-ALPAN	Ozlem	USA	ogokeralpan@oandoalpan.com
GOLEMBO	Myriam	Israel	myriam.golembo@protalix.com
GONZALEZ	Derlis	Paraguay	cote@imperialviajes.com.py
GRAUHOLT	Anne-Marie	Denmark	agrauholt@shire.com
GRINBERG	Yael	Israel	yaelg@szmc.org.il
GUIMARÃES NORONHA	Tatiana	Brazil	tnoronha@bio.fiocruz.br
GUNDOBINA	Olga	Russia	olgound@yandex.ru
GUSINA	Nina	Belarus	nina_gusina@tut.by
HADDAD	Anton	Israel	an_haddad@rambam.health.gov.il
HARUSTOVICH	Iryena	Chile	Iryna.Harustovich@pfizer.com
HASANHODZIC	Mensuda	Bosnia & Herzegovina	info@bcdtravel.rs
HEALES	Simon	United Kingdom	simon.heales@gosh.nhs.uk
HERMAN	Shelly	Israel	shelly.herman@ext.actelion.com
HERRERA MORO CHAO	Daniela	the Netherlands	d.herreramorochao@amc.uva.nl
HLAVATA	Anna	Slovakia	puskasova@continentaltours.sk
HOLLAK	Carla	the Netherlands	c.e.hollak@amc.uva.nl
HONEY	Engela	South Africa	engela.honey@up.ac.za
HOPPER	Melanie	United Kingdom	melanie.hopper@addenbrookes.nhs.uk
HOROWITZ	Mia	Israel	horwitzm@post.tau.ac.il
HUGHES	Derralynn	United Kingdom	rmgvdah@ucl.ac.uk
HYRY	Hanna	United Kingdom	Hannaihyry@gmail.com
IBRICEVIC BALIC	Lejla	Bosnia & Herzegovina	info@bcdtravel.rs
INCERTI	Carlo	USA	carlo.incerti@genzyme.com
IRÚN IRÚN	Maria Pilar	Spain	mpirun@unizar.es
ISH-SHALOM	Sophia	Israel	
IVERSEN	Per Ole	Norway	poeversen@hotmail.com
JANIĆ	Dragana	Serbia	dragana.janic@udk.bg.ac.rs
JARDIM	Erika Ribeiro	Brazil	erjardim@hotmail.com
JIMENEZ	Guillermo	Spain	meetings4@cwt-me.com
JOHNSON	Malcolm	United Kingdom	malcolmdjohnson@hotmail.co.uk
JOVANOVIC	Biljana	Serbia	biljana153@gmail.com
KATZ	Tami	Israel	
KLEIN	Andrés	Israel	adklein@weizmann.ac.il
KLIMKOWSKA	Monika	Sweden	monika.klimkowska@karolinska.se
KNUFF	Catherine	USA	cate.knuff@dealllusconsulting.com
KRIGUER	Doriana	Israel	dorianak@gmail.com
KYRIAZI	Maria	Greece	mariakyriazi@hotmail.com
KYRIY	Tetyana	Ukraine	kirusha9@gmail.com
LAKOCEVIC	Milan	Serbia	info@bcdtravel.rs
LAPATSENTAVA	Alena	Belarus	lapoteutova2005@mail.ru

11th EWGGD, 2014 Haifa PARTICIPANTS LIST			
LAU	Heather	USA	heather.lau4@gmail.com
LAURIDSEN	Anne-Grethe	Denmark	anne-grethe@gaucherforeninger.dk
LE VAN KIM	Caroline	France	caroline.le-van-kim@inserm.fr
LEBEL	Ehud	Israel	lebel@szmc.org.il
LEONARD	Fin	Switzerland	fleonard@shire.com
LEWIS	Drew	USA	drew.e.lewis@pfizer.com
LINKOVA	Lenka	Czech Republic	puskasova@continentaltours.sk
LIZAMA GABRIEL	Tanit	the Netherlands	t.l.gabriel@amc.uva.nl
LOPEZ	Grisel	USA	glopez@mail.nih.gov
LUKINA	Kira	Russia	kira1404@gmail.com
LUNDBLAD	Paulina	Sweden	paulina@attared.se
MacCULLOCH	Alasdair	Switzerland	
MACHACZKA	Maciej	Sweden	maciej.machaczka@ki.se
MACKRELL	Margaret	Canada	margaret.mackrell@sickkids.ca
MAIA	Maria de Lourdes	Brazil	mleal@bio.foicruz.br
MALINOVA	Vera	Czech Republic	puskasova@continentaltours.sk
MAMONOV	Vasily	Russia	bocharova@corptravel.ru
MANKOSKI	Raymond	USA	raymond.mankoski@genzyme.com
MANUEL	Jeremy	United Kingdom	jeremy@eurogaucher.org
MAOR	Gali	Israel	galifit@gmail.com
MARÓDI	László	Hungary	szberndett@tensipecs.hu
MARQUES LORENCO	Charles	Brazil	charlesgenetica@gmail.com
MARTINS	Anna Maria	Brazil	hcp.eventos@flytour.com.br
MARTYNENKO	Mykhailo	Ukraine	zozh@mocz.org.ua
MASSARO	Giulia	United Kingdom	massaro.giu@gmail.com
MAVRIDOU	Eirini	Greece	inchildh@otenet.gr
MEDRANO ENGAY	Blanca	Spain	mbmedrano.iacs@aragon.es
MEEKER	David	USA	david.meeker@genzyme.com
MELLGARD	Bjorn	Switzerland	bmellgard@shire.com
MENGEL	Eugen	Germany	eugen.mengel@unimedizin-mainz.de
MEUTGEERT	Hanka	the Netherlands	h.meutgeert@stofwisselingsziekten.nl
MICHAI	Eliav	Israel	
MICHELAKAKI	Eleni	Greece	inchildh@otenet.gr
MICHIELETTO	Maria Chiara	Italy	mmmchiara877@gmail.com
MISTRY	Pramod	USA	pramod.mistry@yale.edu
MIZRACHI	Itzik	Israel	itzik.mizrachi@actelion.com
MORO	Enrico	Italy	moroe@bio.unipd.it; enrico.moro.1@unipd.it
MORRIS	Elizabeth	United Kingdom	liz.morris@addenbrookes.nhs.uk
MOVSISYAN	Goar	Russia	gongurik@mail.ru
MUCCI	Juan	Argentina	juanmarcosmucci@gmail.com
NASCIMENTO	Ilma	Brazil	ilma.nascimento@pfizer.com
NAVARRETE	Juana	Mexico	juanaban@yahoo.com
NIEMEYER	Pascal	Germany	pascal@eurogaucher.org

11th EWGGD, 2014 Haifa PARTICIPANTS LIST			
NOGUEIRA	Luciana	Brazil	luciananogo2@gmail.com
OLIVIER	Clement	Switzerland	
OŚWIECIŃSKI	Wojciech	Poland	wojtek85@poczta.fm
OZ	Anat	Israel	anato@medison.co.il
PACHECO FERNANDEZ	Natalia	Colombia	nm.pacheco27@uniandes.edu.co
PAGE	Kathleen	United Kingdom	kp429@medschl.cam.ac.uk
PALMON	Nurit	Israel	
PARKKINEN	Johanna	Finland	joparkkinen@gmail.com
PATTERSON	Mary Anne	Canada	mpatterson@mtsinai.on.ca
PAZ	Alona	Israel	
PEÑA ARAGÓN	Carlos David	Mexico	forza_rebel@hotmail.com
PETERSCHMITT	Judith	USA	judith.peterschmitt@genzyme.com
PICKTON	Sarah	United Kingdom	sarahjaypickton@aol.co.uk
PODUSHKINA	Ekaterina	Russia	Ekaterina.podushkina@gmail.com
POGOSYAN	Nelya	Russia	pogosyan.nelik@rambler.ru
POPOVICI	Mariana	Romania	popovici3000@yahoo.co.uk
RACILA	Nina	Rep. of Moldova	ionluka@gmail.com
RAVIV	Mika	Israel	mika102@walla.co.il
REGENBOOG	Martine	the Netherlands	m.regenboog@amc.uva.nl
REINKE	Jörg	Germany	joerg.reinke@unimedizin-mainz.de
RENAULT	Lydie	Switzerland	lrenault@shire.com
ROBERTSON	Andrew	Switzerland	arobertson@shire.com
ROCA ESPIAN	Mercedes	Spain	olga.girona@cwt-me.com
RODIĆ	Predrag	Serbia	predrag.rodic@udk.bg.ac.rs
ROOS	Jonathan	United Kingdom	jonathanroos@cantab.net
ROSENBAUM	Hanna	Israel	h_rosenbaum@rambam.health.gov.il
ROTMAN	Vivian	Brazil	vivian.rotman@bio.fiocruz.br
ROTNER	Mira	Israel	mirar@medison.co.il
ROZENFELD	Paula	Argentina	paularozenfeld@gmail.com
RUBIO	Maria	Mexico	maria.rubio@pfizer.com
SANTILLAN	Yuritzi	Mexico	yuritzisantillan@yahoo.com
SARAIVA-PEREIRA	Maria Luiga	Brazil	mlsaraivapereira@gmail.com
SARMENTO-TRIDADE	Saide Maria	Brazil	saide.trindad@uol.com.br
SCHUIL	Andreas	the Netherlands	andreas.schuil@genzyme.com
SCHWARTZ	Ida Vanessa	Brazil	idaschwartz@gmail.com
SECHI	Annalisa	Italy	sechi.annalisa@aoud.sanita.fvg.it
SERRATRICE	Christine	France	cserratrice@hotmail.fr
SEVITZ	Hylton	South Africa	sevitz@tiscali.co.za
SHAALTIEL	Yoseph	Israel	shaaltiel@protalix.com
SHEMESH	Elad	Israel	elad234@gmail.com
SHURTZ	Shomrat	Israel	shomrats@protalix.com
SIDRANSKI	Ellen	USA	
SIEBERT	Marina	Brazil	marina.s.siebert@gmail.com

11th EWGGD, 2014 Haifa PARTICIPANTS LIST			
SINCA	George	Romania	sinca1george@yahoo.com
SINGH	Manjit	India	manjitsingh@lsdss.org
SKORECKI	Carl	Israel	
SOSARES KERSTENESTZKY	Marcelo	Brazil	marceloskhepato@uol.com.br
SPADA	Marco	Italy	marco.spada@unito.it
STAPELY	Russell	Switzerland	
STRATTON	Kim	Switzerland	kstratton@shire.com
STRISCIUGLIO	Pietro	Italy	pietro.strisciuglio@unina.it
SURREL	Ghislaine	France	
SYSOCOVA	Elena	Russia	epso@mail.ru
SZER	Jeffery	Australia	jli@shire.com; jeff.szer@mh.org.au
SZLAIFER	Mali	Israel	malis@protalix.com
TERREROS	Eduardo	Mexico	etem@prodigy.net.mx
THEOCHARI	Kate	Greece	aik.theochari@yahoo.gr
TIMMERMAN	Jan	the Netherlands	j.timmerman@solcon.nl
TINCHEVA	Radka	Bulgaria	radka.tincheva@gmail.com
TIYOMKIN	Maayan	Israel	palmish@gmail.com
TORQUATI	Fernanda	Italy	info@gaucheritalia.org
TORRALBA	Miguela	Spain	olga.girona@cwt-me.com
TYAGI	Shashank	India	tyagi.shashank1990@gmail.com
TYLEE	Karen	United Kingdom	karen.tylee@cmft.nhs.uk
TYLKI-SZYMANSKA	Anna	Poland	atylki@op.pl
UNDERHILL	Lisa	USA	lisa.underhill@genzyme.com
VAINO	Mariliis	Estonia	mariliisvaino@gmail.com
VAN DONGEN	Patricia	the Netherlands	
VAN EIJK	Marco	the Netherlands	m.c.vaneijk@amc.uva.nl
VAN ZYL	Mollie	South Africa	dr.molliereports@gmail.com
VARDI	Ayelet	Israel	ayalet.vardi@weizmann.ac.il
VASILEVNA ROBU	Maria	Rep. of Moldova	info@bcdtravel.rs
VEERHUIS	Lydia	the Netherlands	a.h.veerhuis@amc.uva.nl
VEGA	Lucia	Chile	angelica.larrain@bcdtravel.cl
VERDIGER	Elad	Israel	
VERHOEK	Marri	the Netherlands	m.verhoek@amc.uva.nl
VILLARUBIA	Jesus	Spain	olga.girona@cwt-me.com
VOM DAHL	Stephan	Germany	stephan.vomdahl@med.uni-duesseldorf.de
VUKOVIC JANKOVIC	Tamara	Serbia	info@bcdtravel.rs
WAGNER	Jasenka	Croatia	jasenkawagner@yahoo.com
WAJNRAJCH	Michael	USA	michael.wajnrajch@pfizer.com
WEISZHUBSHMAN	Monika	Israel	monicawe@clalit.org.il
WELLHOEFFER	Hartmann	Switzerland	hwellhoefer@shire.com
WENGROWER	Zila	Israel	zilaw@medison.co.il
WHITE	Christine	Canada	christinewhite@gauchercanada.ca
WHITE	Katherine	Canada	k.white3@hotmail.com

11th EWGGD, 2014 Haifa PARTICIPANTS LIST			
WIERSMA	Maaike	the Netherlands	m.g.wiersma@amc.uva.nl
WILLIAMS	Aled	Switzerland	awilliams@shire.com
YANKO	Michal	Israel	
YASILEV	Yanco Ivanov	Bulgaria	jnco90@abv.bg
ZAKEN	Hagit	Israel	hagit97@gmail.com
ZARIŅA	Sandra	Latvia	sandra@eurogaucher.org
ZELIG	Zeev	Israel	zelig1@smile.net.il
ZHILIN	Alisa	Israel	a_zhilin@rambam.health.gov.il
ZIGDON	Hila	Israel	hila.zigdon@weizmann.ac.il
ZIMRAN	Ari	Israel	azimran@gmail.com
ZIMRAN	Eran	Israel	eran.zimran@gmail.com
ŽNIDAR	Irena	Slovenia	irena.zni@gmail.com
ZOCCOLI	Joseph	Canada	joseph.zoccoli@pfizer.com

And don't forget your friends at PALEX TOURS

CONFERENCE ORGANIZERS:
PALEX TOURS
Mr. Carel Mayer, Executive Manager
Ms. Lea Keinan, Conference Coordinater

ACKNOWLEDGMENTS

PARTNER OF THE MEETING:

We wish to express our gratitude to the following companies who have helped to make this conference possible: