Abstracts:

All accepted abstracts (oral presentations, rapid communications, and poster-only presentations) are included in this section and are organized by program session.

Oral & Poster Presentations (by Program Session)

Session 1 – Patients' Perspective

O1- Expanding Global Reach: The Impact and Evolution of the International Gaucher Alliance's Global Gaucher Connect Programme (GGCP)

Vesna Aleksovska[1], Tanya Collin-Histed[2], Roselyn Kanja-Odero[3], Alejandra Maria Tornero[4], Patricia Lucki[5], Imalke Kankananarachchi[6], Christian Hendriksz[7], Engela Helena Conradie[8], Albe Swanepoel[8], Jacqueline Emilse Peña[5], Derralynn Hughes[9], Michael Kravchyna[10], Dustin O'Dell[10]

[1]International Gaucher Alliance, Bitola, Republic of North Macedonia; [2]International Gaucher Alliance, London, United Kingdom; [3]International Gaucher Alliance, Nairobi, Kenya; [4]International Gaucher Alliance, Buenos Aires, Argentina; [5]International Gaucher Alliance, Guatemala; [6]Rare Disease Forum, Sri Lanka College of Paediatricians, Colombo, Sri Lanka; [7]A Rare Cause, Registered charity in England and Wales, Ilkley, United Kingdom; [8]Centre for Human Metabolomics, Desmond Tutu School of Medicine, Faculty of Health Sciences, North-West University, Potchefstroom, South Africa; [9]Royal free London NHS foundation trust and University College, London, United Kingdom; [10]SymetryML, Morristown, NJ, United States

Presentation type: Oral Presentation
Poster number: P1 - **Tergeste** Room

The International Gaucher Alliance (IGA) is dedicated to advancing global equity and improving outcomes for Gaucher patients through its Global Gaucher Connect Programme (GGCP). This initiative is strategically designed to support communities in regions where there are no established patient organisations, with a core mission to facilitate early diagnosis, adequate medical care, and effective disease management.

A critical component of this effort is the Humanitarian Aid Programme, which, in collaboration with pharmaceutical partners, provides access to life-saving treatments otherwise unavailable through local healthcare systems. The GGCP's work is multifaceted, encompassing the development of in-country patient registries, capacity-building webinars for healthcare professionals, and the establishment of local patient advocacy networks. Currently, the GGCP is active in Africa, Central Latin America, and South Asia.

The programme's strategic framework is built on five key objectives: strengthening data collection and analysis to inform patient care and treatment outcomes; intensifying advocacy

for policy changes on access, reimbursement, and genetic testing; expanding capacity-building resources for healthcare professionals and caregivers; fostering crucial collaborations with other organisations and pharmaceutical partners; and developing sustainable funding models.

A defining element of this initiative is the powerful collaboration with the International Working Group on Gaucher Disease (IWGGD) and A Rare Cause (ARC). This partnership, along with the invaluable support of volunteers, allows the IGA to deliver educational programmes that directly address significant healthcare challenges in underserved areas. These challenges include limited diagnostic resources, low disease awareness, and restricted treatment access. This proactive, sustained cooperation enables the IGA to act as a facilitator and enabler, providing essential support and achieving better results in communities most in need.

Conflict of Interest: C.H. is CMO and co-founder of Decentra Health. V.A. and T.C.H. report annual work programme grants for the International Gaucher Alliance from Amicus, ISU Axbis, AceLink Therapeutics, Pfizer, Sanofi, Takeda, Spur Therapeutics, Lilly and M6P; T.C.H. has also received consulting fees and meeting support from Takeda and Sanofi. D.H. has received honoraria for advisory boards and educational meetings from Sanofi, Takeda and Spur Therapeutics. M.K. and D.O. are employees of SymetryML. All other authors declare no conflicts of interest.

O2- Different diseases, different needs: Patient preferences for gene therapy and beliefs about prescribed medications vary in lysosomal storage diseases

Eleonore M. Corazolla[1], Eline C.B. Eskes[1], Jorien Veldwijk[1], Marion M.M.G. Brands[1], Hanka Dekker[1], Erica van de Mheen[1], Mirjam Langeveld[1], Carla E.M. Hollak[1], Barbara Sjouke[1]

[1]Amsterdam UMC location University of Amsterdam, Endocrinology and Metabolism, Amsterdam, Netherlands

Presentation type: Oral Presentation
Poster number: P2 - **Tergeste** Room

Gene therapy is being developed for lysosomal storage diseases with different current therapeutic options. We compare gene therapy-related risk tolerance and beliefs about current medications between people affected by three lysosomal storage diseases with different therapeutic options and prognoses.

We combined choice experiments on participants' risk tolerance regarding gene therapy using the probabilistic threshold technique and the Beliefs in Medicine Questionnaire in which participants are grouped in attitudinal categories.

Adults with Gaucher disease type 1, Fabry disease, and parents of children with mucopolysaccharidosis type III A/B completed 85 surveys. Gaucher disease respondents preferred the current standard of care and were mostly accepting of their current medication. MPS III representatives were more risk tolerant and indifferent towards their child(ren)'s current medication. Male Fabry disease participants were more risk tolerant than females and mostly ambivalent or accepting towards current medication. Female Fabry disease participants were almost equally distributed over all belief categories.

In conclusion, beliefs about current therapy options and risk tolerance regarding gene therapy align with unmet medical needs in lysosomal storage diseases. Embedding this approach of analysing patient preferences into the development process of new therapies may improve their alignment with recipients' needs.

Conflict of Interest: M.L. and C.H. are involved in pre-marketing studies with Sanofi and Chiesi. B.S. has been involved in pre-marketing studies with Protalix, Chiesi, Sanofi-Genzyme and Reneo Pharmaceuticals, none of which were related to the content of this study. All other authors declare no conflicts of interest.

O3- Guidelines on Home Therapy in Gaucher Disease

Tanya Collin-Histed[1], **Carolina Toneloto[2]**, Vesna Aleksovska[3], Angel Jones[1], Sintia Tamele[4], Shoshana Revel-Vilk[5], Irena Znidar[6], Fernanda Torquati[7], Kristiyan Dimitrov[8], Magy Abdelwahab[9], Michaela Dan[10], Sara Khan[1], Karoline Stepien[11], Christine Serratrice[12], Uma Ramaswami[13], Beata Kieć-Wilk[14], Majdolen Istaiti[15], José Luis Mosso Lara[16,17]

[1]International Gaucher Alliance, London, United Kingdom; [2]International Gaucher Alliance, Sao Paulo, Brazil; [3]International Gaucher Alliance, Bitola, Republic of North Macedonia; [4]Associação Moçambicana de Doenças Raras (AMODORA). Mozambique; [5]Gaucher Unit, The Eisenberg R&D Authority, Shaare Zedek Medical Center, Jerusalem, Israel; [6]International Gaucher Alliance, Ljubljana, Slovenia; [7]International Gaucher Alliance, Florence, Italy; [8]International Gaucher Alliance, Bulgaria; [9]Cairo University Pediatric Hospital, Kasralainy hospital, Egypt; [10]French Gaucher Diseases Expert Group (CETG), France; [11]Salford Royal Hospital, Northern Care Alliance NHS Foundation Trust, United Kingdom; [12]University Hospital of Geneva. Switzerland; [13]Royal Free Hospital and University College London, United Kingdom; [14]Unit Rare Metabolic Diseases, Jagiellonian University Medical College, Krakow, Poland; [15]Department of Endocrinology and Metabolism, Amsterdam UMC, Amsterdam, The Netherlands; [16]London School of Hygiene and Tropical Medicine, London, United Kingdom; [17]Anahuac Mexico School of Medicine, Mexico City, Mexico

Presentation type: Oral Presentation
Poster number: P3 - **Tergeste** Room

Home-based enzyme replacement therapy (ERT) for Gaucher disease (GD) is an established practice in many countries and gained renewed importance during the COVID-19 pandemic, when maintaining continuity of care became challenging. In response, the International Gaucher Alliance (IGA) and the International Working Group on Gaucher Disease (IWGGD) jointly developed multidisciplinary guidelines to support the safe and effective delivery of disease-modifying infusions outside traditional healthcare settings. The guideline provides recommendations for clinicians, nurses, pharmacists, home-care providers, patients, and caregivers, covering clinical, logistical, and organizational aspects of home infusion programs.

Evidence from the literature shows that home therapy for GD is safe, feasible, and associated with high patient satisfaction, better quality of life, and decreased use of hospital resources. Infusion-related reactions are uncommon and usually occur during initial hospital-based doses; with appropriate training and monitoring, treatment can subsequently be administered at home. Clinicians oversee safety, adherence, and follow-up, while nurses, pharmacists, distributors, and patients share responsibilities for preparation and administration.

A 2022 international survey of IGA member organizations found that home therapy was available in 62.5% of responding countries. Key barriers include insufficient legislation, governmental restrictions, and logistical challenges. Respondents highlighted that guidelines, best-practice sharing, risk–benefit information, and advocacy tools would support broader implementation. Reported advantages of home therapy included reduced travel and waiting time, more flexible scheduling, and improved continuity of care; drawbacks involved confidentiality concerns, storage of materials, and delivery logistics.

Home therapy also provides economic advantages. For payers, it reduces costs associated with hospital infusion rooms and staff, while for patients it lowers travel expenses and treatment burden.

This review will serve the basis for developing an educational leaflet aimed at patients, families, and healthcare professionals, offering clear and accessible guidance to support safe and effective home infusions worldwide.

Conflict of Interest: V.A., T.C.-H., and I.Z. report annual work programme grants for the International Gaucher Alliance (IGA) in 2023–2025 from Amicus, ISU Axbis, AceLink Therapeutics, Pfizer, Sanofi, Takeda, Spur Therapeutics, Lilly and M6P; T.C.-H. has also received consulting fees and meeting support from Takeda and Sanofi. S.R.-V. reports that the SZMC Gaucher Unit receives support from Sanofi for participation in the ICGG Registry and from Takeda for the GOS Registry; S.R.-V. has also received honoraria, travel support and advisory fees from Takeda and Sanofi. C.S. has received grant/research support, honoraria and advisory fees from Sanofi/Genzyme and Takeda. All other authors declare no conflicts of interest.

Session 2 – Laboratory: Genetics & Biochemistry

O4- Beyond Sequence Homology: Dissecting Complex Alleles and Epigenetic Landscapes at the GBA1–GBA1LP Locus via Native DNA Nanopore Long-Read Sequencing

Natascha Bergamin[1,2], Paolo Peruzzo[1], Silvia Cattarossi[1,2], Emma Cuttini[1], Eleonora Pavan[1], Maximiliano Ormazabal[1], Maurizio Scarpa[1], Andrea Dardis[1]

[1]Regional Coordinator Center for Rare Diseases, University Hospital of Udine, Italy; [2]Department of Laboratory Medicine, University Hospital of Udine, Italy

Presentation type: Oral Presentation
Poster number: P11 - **Giusto** Room

Background: Biallelic pathogenic variants in GBA1 cause Gaucher disease (GD), while heterozygous carrier status represents a major genetic risk factor for Parkinson's disease (PD) and Lewy body dementia. Molecular diagnosis of GBA1-related disorders is technically challenging due to the highly homologous pseudogene GBA1LP. The high homology and proximity between the gene and pseudogene increase the frequency of recombination events, generating complex alleles or deletions not easily detectable with Next-Generation short-read Sequencing (NGS).

To date, accurate GBA1 genotyping necessitates an integrated approach involving sequencing of gene-specific (Long-range) PCR amplicons and MLPA analysis to complement NGS data.

Aim: To determine whether long-read sequencing could overcome the read alignment challenges between GBA1 and GBA1LP that compromise short-read accuracy, we developed a targeted Oxford Nanopore Technology (ONT) protocol to simplify and accelerate the molecular diagnosis of GD and GBA1 carrier detection.

Methods: DNA from Gaucher patients carrying challenging complex alleles and/or single nucleotide pathogenic variants, was analyzed using an "adaptive sampling" strategy to enrich for the locus encompassing GBA1 and GBA1LP without the need of PCR amplification.

Results: The developed method successfully reconstructed all patients' genotypes, including complex alleles missed by short reads NGS methods. Furthermore, it enabled haplotype definition, variant phasing and locus methylation analysis without additional experiments, significantly reducing turnaround times. Furthermore, simultaneous analysis of both the GBA1-GBA1LP locus from native DNA, facilitated the differentiation of fusion, conversion, and deletion events providing information that may improve genotype-phenotype correlations, since some authors suggest that cross-over between GBA1, GBA1LP or contiguous genes may contribute to modulate phenotype.

Conclusions: Targeted long-read sequencing using native DNA, provides a streamlined, single-assay solution for comprehensive GBA1 characterization, eliminating the need for multiple complementary techniques. This approach improves diagnostic efficiency and enables detailed structural variant analysis that may contribute to a better understanding of phenotypic variability in GD.

Conflict of Interest: None declared.

O5- Elevated soluble ACE2 in Gaucher patients - an evolutionary advantage?

Ahmad Fokra[1], Hagit Baris Feldman[2,3], Alina Kurolap[2], Safa Kinaneh[1], Zaid Abassi[1,4] and **Tova Hershkovitz[5,6]**

[1]Department of Physiology and Biophysics Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel; [2]The Genetics Institute and Genomics Center, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel; [3]Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel, [4]Laboratory Medicine, Rambam Health Care Campus, Haifa, Israel; [5]The Genetics Institute, Rambam Health Care Campus and Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel; [6]Institute of Human Genetics, Galilee Medical Center, Nahariya, Israel.

Presentation type: Oral Presentation
Poster number: P12 - **Giusto** Room

Objectives: Gaucher disease (GD) has a high carrier rate among Ashkenazi Jews, although the most common disease-causing variant, N370S, is pan-ethnic. This has led to speculations of evolutionary advantage for carriers, particularly of this variant. Indeed, during the recent COVID-19 pandemic, GD patients reportedly had a surprisingly low infection rate and mild symptoms considering their disease status. As SARS-CoV-2 gains entry into the cell via membrane-bound angiotensin-converting enzyme 2 (ACE2), we speculated that differences in levels of soluble ACE2 in GD patients could contribute to this protective state. While ACE is a biomarker of GD, ACE2 levels have not been explored in GD.

Methods: We measured serum levels of ACE and ACE2 by ELISA in 33 GD patients and 17 age- and sex-matched controls as well as macrophage bound ACE2 by western blot, in 7 GD and 7 age- and sex-matched controls.

Results: Our results revealed a significant elevation of both serum and macrophage-bound ACE and ACE2 in GD patients compared to healthy controls. Moreover, the most robust ACE2 elevation was observed in N370S homozygotes (60ng/ml in homozygotes versus 20ng/ml in controls; $P \leq 0.001$.), which was not influenced by GD treatment.

Conclusions: We provide preliminary evidence for significant soluble ACE2 elevation in GD patients, particularly those with the N370S homozygous genotype. Since coronaviruses use the ACE2 receptor as a gateway for host cell entry, we speculate that elevated circulating ACE2 may

serve as a decoy, giving advantage to GD patients during viral infections, of which SARS-Cov-2 serves as a contemporary example.

Conflict of Interest: None declared.

O6- Glucosylated phytosterols: a new player in Gaucher disease?

Johannes M.F.G. Aerts[1], Kate Bila[1], Stef Bannink[1], Majdolen Istaiti[2], Carla Hollak[2]

[1]Department Medical Biochemistry, Leiden Institute of Chemistry, Leiden University, Leiden, The Netherlands, [2]Department of Endocrinology and Metabolism, Amsterdam UMC, Amsterdam, The Netherlands.

Presentation type: Oral Presentation
Poster number: P13 - **Giusto** Room

Phytosterols (sitosterol, campesterol, stigmasterol) are cholesterol analogues in plants. Glucosylated forms of several phytosterols are known to occur. Even 6-O-acylated Glc versions of these structures. Glucosylated phytosterols seem to be well absorbed. Given our recent finding that 6-O-acyl-Glc-β-methylumbelliferyl is an excellent substrate for glucocerebrosidase (GCase)[1], the enzyme deficient in Gaucher disease (GD), we studied using advanced mass spectrometry with synthesized 13C encoded internal standards, the presence of (6-O-acyl)-glucophytosterols in GD patients and normal individuals. Increased levels of various glycophytosterols were observed in GD plasma specimens. Likewise, increased (O acyl)glucophytosterols were detected in spleens from type 1 GD patients.

Our findings are a novum: an exogenous substrate for a lysosomal enzyme (GCase) accumulating in corresponding (GD) patients. Of interest, glucophytosterol accumulation may be not trivial: exposure of rodents to glucophytosterols induces the full spectrum of Parkinson disease symptoms[2]. Glucophytosterols might be an additional factor linking GBA1 deficiency with GBA-PD[3].

References:
[1]Bannink S, Bila KO, et al. J Lipid Res. 2024 Nov;65(11):100670.
[2]Van Kampen JM, et al. EPMA J. 2017 Sep 4;8(3):261-271.
[3]Sidransky E, et al. N Engl J Med. 2009 Oct 22;361(17):1651-61.

Conflict of Interest: None declared.

O7- Immune and Inflammatory Signatures in Gaucher Disease: Implications for Gene and Precision Therapies.

Margarita Ivanova[1], Julia Dao[1], Lauren Noll[1], and Ozlem Goker-Alpan[1]

[1]Lysosomal and Rare Disorders Research and Treatment Center

Presentation type: Oral Presentation
Poster number: P14 - **Giusto** Room

Background: Gaucher disease (GD), caused by pathogenic variants in the *GBA1* gene, is recognized as a lysosomal disorder with immune activation. Glucosylceramide and glucosylsphingosine accumulate in macrophages, triggering chronic inflammation and altering

the function of lymphocytes and monocytes. These changes can affect both disease presentation and responses to gene therapy (GT).

Methods: We assessed cytokine and immune profiles in five patients with type 1 GD enrolled in gene therapy (GT) trials using different vectors. Plasma samples were analyzed at baseline and at 1 to 12 months after therapy (IRB-NCT02000310) using a 72-plex Luminex assay. We compared changes in markers of the innate immune system (IL-1β, IL-6, TNF-α, MCP-1), adaptive immune system (IFN-γ, IL-17, IL-12p70), and angiogenesis (FGF2, PDGFs, VEGF-A), as well as antibodies to exogenous GCase.

Results: Baseline cytokine profiles in GD patients varied significantly, displaying a unique inflammatory signature. The most pronounced macrophage-driven inflammation, characterized by elevated IL-12p40, GM-CSF, MCP-1, MIP-1α, and VEGF-A, has been observed. After GT, all patients experienced transient innate immune activation (increased IL-2, IL-6, IL-1α, IFN-γ, IFN-α2) within 1-3 weeks, but levels normalized by 12 months. Patient 2 exhibited the highest cytokine peaks at 3 months, particularly for GROα, TPO, IL-12p70, and Eotaxin-3. No chronic inflammation, sustained adaptive response, or long-term antibody persistence was detected.

Conclusion: GD features a primed but self-regulating immune system, driven by chronic macrophage activation and lysosomal dysfunction. Despite variable baseline inflammatory signatures, GT induced only brief cytokine activation, which resolved within 12 months; no ongoing humoral reactivity or chronic inflammation was observed. These findings highlight the need for immune monitoring in GD and support the immunologic tolerability and safety of AAV-based therapies in this population.

Conflict of Interest: None declared.

O8- When glucosylsphingosine does not normalize: pharmacogenetic determinants of biochemical–clinical dissociation during eliglustat therapy

Sonia Roca-Esteve[1], Irene Serrano-Gonzalo[1], Isidro Arévalo-Vargas[1], Carlos Lahoz-Gil[1], Laura Lopez de Frutos[1], Pilar Giraldo[1]

[1]Fundación Española para el Estudio y Terapéutica de la Enfermedad de Gaucher

Presentation type: Oral Presentation
Poster number: P15 - **Giusto** Room

In Gaucher disease type 1 (GD1), glucosylsphingosine (GluSph) is a highly specific biomarker, typically declines rapidly after treatment, paralleling improvements in visceral volumes and hematologic parameters. Eliglustat, an oral substrate reduction therapy, shows robust biochemical and clinical efficacy. However, many patients maintain elevated GluSph levels despite long-term treatment and good adherence, raising questions about therapeutic adequacy and the need for treatment adjustment, given its pro-inflammatory and potentially toxic role.
To evaluate the relationship between post-treatment GluSph levels and individual CYP2D6 activity score in GD1 patients receiving eliglustat.
We analyzed 109 GD1-patients included in the Spanish Gaucher Disease Registry who were treated with eliglustat. Patients were classified according to CYP2D6 phenotype and activity score following Gaedigk et al. (J Pers Med, 2018). GluSph concentrations at 1-year and ≥5-year

follow-up were assessed in relation to age, sex, GBA1 genotype, concomitant medications, hepatic and renal function, additional biomarkers, and hematologic and visceral responses. The mean (range) age of patients included was 44.3 (18-80) years, 54 females and 55 males. . CYP2D6 phenotypes were distributed as follows: 87 normal, 14 intermediate, and 6 poor metabolizers (ultrarapid metabolizers excluded). Activity scores ranged from 0 to >2 (S0: 6; S0.5: 13; S1: 25; S1.5: 18; S2: 45; S>2: 2). Among the 60 patients treated for ≥5 years, 33.3% exhibited persistent GluSph elevations of 2–3-fold above the upper normal limit, despite stable hematologic parameters and sustained visceral response. Persistent elevation was enriched among patients with lower CYP2D6 activity scores. Additional genotype- and biomarker-based correlations will be presented.
Persistent elevation of GluSph during long-term eliglustat therapy is associated with CYP2D6 activity score and does not necessarily reflect clinical or visceral treatment failure. These findings support a pharmacogenetically informed GluSph interpretation and caution against modifying treatment based solely on an isolated biomarker elevation in otherwise stable GD1 patients.

Conflict of Interest: P.G. receives research grants from Sanofi and Takeda. All other authors declare no conflicts of interest.

Session 3 – Gaucher Disease Clinical Spectrum

O9- Perinatal-Lethal Gaucher Disease: Clinical, Biochemical and Pathological Insights from 15 French Cases

Camila Rochet-Capellan[1], Roseline Froissart[1], Sophie Collardeau-Frachon[1], **Magali Pettazzoni[1]**

[1]Hospices Civils De Lyon

Presentation type: Oral Presentation
Poster number: P62 - Zodiaco Room

Introduction: Perinatal-lethal Gaucher disease (PLGD) represents the rarest and most severe manifestation of Gaucher disease, accounting for <1% of cases. Caused by biallelic pathogenic variants in GBA1 gene, PLGD leads to profound glucocerebrosidase deficiency and massive prenatal glucosylceramide and lysoglucosylceramide accumulation. Its phenotypic spectrum remains insufficiently characterized. We report a comprehensive retrospective analysis of all PLGD cases diagnosed in our national reference laboratory over 20 years.

Methods/ Results: Fifteen fetuses (including one sibling pair) were diagnosed between 2002 and 2025. Diagnosis was established prenatally in most cases but required fetopathological examination in one fetus and was made retrospectively in another following the birth of an affected sibling. The mean gestational age at suspicion was 26.5 weeks of gestation. Pregnancy outcomes included intrauterine fetal death in 8/15 cases and medical termination in 7/15. Parental consanguinity was documented in seven families.

Prenatal ultrasound commonly revealed hydrops (12/15), with associated ascites (4/12), reduced fetal movements (7/15), and arthrogryposis (2/15). Additional findings included IUGR (3/15), hepatomegaly (5/15), splenomegaly (1/15), and neurological abnormalities in 10/14 fetuses—primarily cerebellar hypoplasia and corpus callosum anomalies.

Fetopathology (12 cases) consistently confirmed extensive hydrops features, hepatomegaly (10/12), splenomegaly (12/12), limb deformities (11/12), and pulmonary hypoplasia (8/12). Microscopy demonstrated widespread Gaucher cell infiltration. Brain examination (8 cases) revealed predominant microcephaly, cerebellar hypoplasia, and cortical malformations.

Biochemical testing showed markedly reduced GCase activity in all cases. Lysoglucosylceramide was markedly elevated in all tested amniotic fluid samples. GBA1 genotyping (by Sanger sequencing) identified biallelic pathogenic variants in the 12 families tested. In one case, prenatal exome sequencing returned falsely normal.

Conclusion: PLGD is an exceptional but distinctive cause of non-immune hydrops. Recognition of its characteristic triad—hydrops, arthrogryposis, and hepatosplenomegaly—combined with targeted enzymatic, biomarker and genetic testing enables timely diagnosis, critical for counselling and the management of future pregnancies.

Conflict of Interest: None declared.

O10- Lyso-Gb1 Dynamics in Untreated Patients with Gaucher Disease

Tama Dinur[1], Ari Zimran[1,2], Elena Schulman[1], Dafna Frydman[1], Michal Becker-Cohen[1], **Shoshana Revel- Vilk**[1,2]

[1]Gaucher Unit, The Eisenberg R&D Authority, Shaare Zedek Medical Center, Jerusalem, Israel;[2]The Faculty of Medicine, Hebrew University, Jerusalem, Israel

Presentation type: Oral Presentation
Poster number: P63 - **Zodiaco** Room

Background: Lyso-Gb1 is widely used as a biomarker for monitoring disease activity in Gaucher disease (GD). While treatment-related reductions in lyso-Gb1 are well documented, the natural trajectory of lyso-Gb1 levels during untreated periods remains poorly characterized. Understanding this variability may help clinicians interpret biomarker changes and guide treatment decisions in routine clinical practice.

Methods: Our GD unit maintains a longitudinal database of approximately 700 patients contributing more than 6,200 visits with recorded lyso-Gb1 measurements. Patients with at least two visits during untreated periods were included in the trend analysis (n=277), with a median follow-up time of 6 years. Predefined thresholds for clinically meaningful changes were ≥50 ng/mL for lyso-Gb1, ≥50×10^9/L for platelet count, and ≥1 g/dL for hemoglobin. Logistic regression analysis was performed to identify predictors of increases or decreases in lyso-Gb1 during untreated follow-up.

Results: During untreated periods, 40 patients (14.4%; 95% CI 10.6–19.3%) demonstrated a decline in lyso-Gb1 levels. The median decrease was 94.8 ng/mL (range 50.5–394), and in 17 patients the decline exceeded 100 ng/mL. Declines were more frequent in females (p=0.02) and were associated with higher baseline lyso-Gb1 levels (p<0.001). Age, genotype severity, baseline hemoglobin, and platelet count were not significant predictors. An increase in lyso-Gb1 was observed in 97 patients (35%; 95% CI 29.5–40.5%), with a median rise of 127 ng/mL (range 52–724). Increases were associated with younger age (p=0.03), lower baseline hemoglobin (p=0.03), and lower platelet counts (p<0.001). No significant association was observed between changes in lyso-Gb1 and concurrent changes in hematologic parameters.

Conclusions: Among untreated GD patients, spontaneous declines in lyso-Gb1 are uncommon but can occur. Increases were more frequent and tended to occur in patients with markers of more severe disease. However, most untreated patients remained stable within ±50 ng/mL over time, likely reflecting a milder phenotype and slower disease progression.

Conflict of Interest: The SZMC Gaucher Unit receives support from Sanofi/Genzyme for participation in the ICGG Registry and from Takeda for the GOS Registry. A.Z. receives honoraria from Takeda, Pfizer, and BioEvents and consultancy fees from Takeda, NLC Pharma, Insightec, and Prevail therapeutics is employed by the company Agyany pharma. S.R.-V. receives grant/research support, honoraria, and advisory fee from Takeda, Pfizer, and Sanofi/Genzyme. All others- none declared.

O11- Gaucher Disease type 1 in Elderly Individuals: A Systematic Review

Julia Cordeiro Milke[1,2], Eduardo Augusto Schütz[3], Arthur Minas Alberti[4], **François Maillot[5,6]**, Ida Vanessa Doederlein Schwartz[1,2,3]

[1]InRaras, Brazilian National Institute on Rare Diseases, Porto Alegre, Brazil; [2]Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil; [3]Federal University of Rio Grande Do Sul, Porto Alegre, Brazil; [4]Federal University of Health Sciences, Porto Alegre, Brazil; [5]Department of Internal Medicine, University Hospital of Tours, Tours, France; [6]University of Tours, Tours, France

Presentation type: Oral Presentation
Poster number: P64 - **Zodiaco** Room

Introduction: Gaucher Disease (GD) is an inborn error of metabolism characterized by the accumulation of glucocerebrosides due to deficiency of acid β-glucosidase. Although GD type 1 can be diagnosed in any age, cases can be identified in elderly patients, presenting additional diagnostic challenges, as the clinical findings may overlap with other prevalent disorders in this population. Aims: To characterize the clinical presentation and diagnosis of GD in older patients (≥ 65 years).

Methods: A systematic review of the literature was conducted in PubMed, Embase, Lilacs and Web of Science up to September 2025, using MESH terms for “Gaucher Disease”, “aged” and “diagnosis”. Inclusion criteria comprised: 1) case reports, case series, cohort studies, systematic reviews; AND 2) GD diagnosed with ≥ 65 years old. The extracted data included information on age at diagnosis, age at symptom onset, sex, family history, consanguinity and clinical manifestations.

Results: The search yielded 1,813 articles, 76 were preselected and 27 articles were included after full-text review, reporting 26 patients (M = 15). The median age at diagnosis was 71 years old (65-85 years), and the ages at onset of symptoms ranged from 19-82 years. The most frequent clinical manifestations were splenomegaly (n=17), thrombocytopenia (n=9), anemia (n=9), hepatomegaly (n=9) and mucocutaneous bleeding (n=8). Positive family history was reported in three cases, with no consanguinity reported.

Discussion: The findings demonstrate that GD can be diagnosed in elderly individuals, even when symptoms begin earlier. The diversity of affected clinical systems underscore the need for a comprehensive evaluation, particularly of hematological manifestations. Early recognition is essential for the initiation of disease-specific therapies, suggesting that professionals should maintain a high diagnostic suspicion and consider metabolic investigations as part of the differential diagnosis in older adults.

Conflict of Interest: None declared.

O12- Development and Validation of an Age-Adapted Disease Severity and Burden Scoring System for Neuronopathic Gaucher Disease (nGD/GD3)

Leah Svarney[1], Sara Mitchell[1], Bobby Sandhu[1], and **Ozlem Goker-Alpan**[1]

[1]Lysosomal and Rare Disorders Research and Treatment Center

Presentation type: Oral Presentation
Poster number: P65 - Zodiaco Room

Background: Neuronopathic Gaucher disease (nGD), including type 3 (GD3), exhibits marked clinical heterogeneity across neurologic, systemic, skeletal, and developmental domains. Existing assessment tools inadequately capture disease complexity across ages and fail to distinguish current medical severity from longitudinal disease burden, limiting their utility in clinical trials and longitudinal care.

Methods: We developed a comprehensive, age-adapted nGD/GD3 Disease Severity and Burden Scoring System (DSBS) through expert consensus and iterative clinical validation. The system integrates ordinal scoring across neurologic, systemic, skeletal, and developmental domains, with age applicability. Pulmonary involvement is graded incorporating imaging and pulmonary function testing. Cognition, behavior/psychiatric manifestations, and functional independence are assessed as distinct constructs. A complementary Burden Index (BI) contextualizes severity by incorporating age at onset, disease trajectory, functional dependency, caregiver burden, and treatment response. Severity Score (SSV) and BI are interpreted alongside clinician global impression (CGI).

Results: Pilot application across pediatric and adult nGD patients demonstrated that the DSBS reliably differentiates mild, moderate, and severe neurologic disease while accurately capturing high disease burden in individuals with preserved cognition but significant behavioral or functional impairment. The separation of severity and burden prevented over-classification of disease severity in patients with neurobehavioral phenotypes while appropriately identifying advanced multisystem disease. Alignment between SSV, BI, and CGI was preserved across heterogeneous clinical presentations.

Conclusions: The nGD/GD3 DSBS provides a clinically intuitive, scalable, and trial-ready framework for assessing disease severity and burden across the lifespan. By separating medical severity from functional and caregiver burden, this system supports longitudinal monitoring, natural history studies, and clinical trials in neuronopathic Gaucher disease.

Conflict of Interest: None declared.

O13- Risk and Prevalence of Overweight and Obesity Among Adults with Gaucher Disease

Tama Dinur[1], **Ari Zimran**[1,2], Elena Schulman[1], Dafna Frydman[1], Michal Becker-Cohen[1], Shoshana Revel- Vilk[1,2]

[1]Gaucher Unit, The Eisenberg R&D Authority, Shaare Zedek Medical Center, Jerusalem, Israel;[2] The Faculty of Medicine, Hebrew University, Jerusalem, Israel.

Presentation type: Oral Presentation
Poster number: P66 - Zodiaco Room

Background: Weight gain and obesity have become increasingly recognized in Gaucher disease (GD), particularly among patients receiving enzyme replacement therapy (ERT). Characterizing prevalence and determinants of weight trajectories is important for optimizing long-term outcomes and informing comprehensive management.

Methods: We analyzed longitudinal height and weight data (1991–April 2025) from all adults with GD (≥18 years). Body mass index (BMI), sex, genotype severity, and treatment status were extracted from electronic records. Annualized changes in weight and BMI were calculated and adjusted for age, sex, and follow-up duration.

Results: The cohort included 574 adults (55% female) with at least two anthropometric measurements. The median age at the first follow-up was 28.5 years (range 18–87); 65.5% had a mild genotype (N370S homozygous). Treatment groups included those receiving ERT (n=108), those who were untreated (n=182), and those who received non-consistent therapy during follow-up (ERT, substrate reduction therapy, or no treatment; n=284). No significant differences in median weight or BMI change (from first to last measurement) were observed among these three groups after adjusting for age, sex, and follow-up duration. However, annualized BMI and weight gain were significantly higher in patients treated with ERT than in untreated patients ($p<0.001$). The prevalence of overweight (BMI >25) and obesity (BMI >30) was 42.3% and 23.2%, respectively, with no differences related to treatment status. Thirty-nine individuals (6.7%, 95% CI 4.9%-9.2%) developed Obesity Class II or III, which was associated only with higher baseline weight and BMI.

Conclusions: Overweight and obesity are common in GD, with prevalence similar to the general population. While treatment status was not associated with overall prevalence, ERT was linked to higher annualized weight gain. Severe obesity was predicted primarily by baseline anthropometrics. These findings underscore the need for early risk detection and lifestyle intervention in GD and highlight the importance of monitoring potential metabolic effects of long-term therapy.

Conflict of Interest: The SZMC Gaucher Unit receives support from Sanofi/Genzyme for participation in the ICGG Registry and from Takeda for the GOS Registry. A.Z. receives honoraria from Takeda, Pfizer, and BioEvents and consultancy fees from Takeda, NLC Pharma, Insightec, and Prevail therapeutics is employed by the company Agyany pharma. S.R.-V. receives grant/research support, honoraria, and advisory fee from Takeda, Pfizer, and Sanofi/Genzyme. All others- none declared.

O14- An AI-Driven Multilayer Model of Lung Involvement in Neuronopathic Gaucher Disease (nGD): Validation in a 45-Patient Cohort and Implications for Management

Sara Mitchell[1], Leah Svarny[1], Bobby Sandhu[1], Ozlem Goker-Alpan[1]

[1]Lysosomal and Rare Disorders Research and Treatment Center

Presentation type: Oral Presentation
Poster number: P38 - **Giusto** Room

Background: Pulmonary involvement in neuronopathic Gaucher disease (nGD) is frequently severe and heterogeneous, extending beyond Gaucher cell infiltration to include immune dysfunction, recurrent infections, aspiration injury, and pulmonary vascular remodeling. Using an AI-assisted integrative framework, we developed a multilayer pathogenic model and evaluated its validity using clinical data from a 45-patient GD2/GD3 cohort. We further mapped therapeutic strategies to each pathogenic layer to guide mechanism-based management.

Methods: An AI-guided synthesis of mechanistic literature, immunologic pathways, and radiologic patterns generated a five-layer model of pulmonary pathology. Clinical validation was performed using data from 45 individuals with GD2/GD3, including Lyso-Gb1 levels, chest imaging, pulmonary function tests (PFT), infection history, and aspiration risk. Cohort findings were compared against predicted substrate-driven, immune-metabolic, infectious, aspirational, and vascular elements of the model.

Results: Patients demonstrated significant disease and substrate burden, with Lyso-Gb1 levels commonly >100 ng/mL. Imaging showed ground-glass opacities, reticulonodular changes, and asymmetric perihilar infiltrates. PFTs revealed DLCO reductions, indicating early vascular and interstitial injury consistent with PVOD-like remodeling. Recurrent infections were widespread, confirming immune vulnerability. Aspiration was documented in one-third of patients and strongly correlated with persistent and asymmetric radiologic abnormalities. The overall pattern validated the AI-derived multilayer model integrating substrate overload, lung cell dysfunction, immune dysregulation, external injury, and vascular remodeling.

Conclusion: This AI-driven model accurately reflects real-world nGD lung disease and provides a practical mechanism-based framework for risk stratification and targeted management. The multilayer model supports a staged, mechanism-aligned approach, which is crucial for optimizing outcomes and includes: disease specific management with ERT, high-dose ambroxol, or SRT target substrate burden. Immune-modulating oral agents with pediatric use address inflammation, autophagy impairment, and oxidative injury. Targeted biologics may benefit selected patients with severe inflammatory phenotypes. Aspiration mitigation and infection prevention, and monitoring and treating pulmonary hypertension address further downstream consequences.

Conflict of Interest: None declared.

Session 4 – Laboratory: Basic Research

O15- Evaluation of dopaminergic neurons from isogenic iPSC lines derived from a donor with Gaucher disease and Parkinson disease reveal the role of GPNMB in GBA1-associated parkinsonism

Yu Chen[1], Chase Chen[1], Charis Ma[1], **Ellen Sidransky**[1]

[11]National Institutes of Health, Unites States

Presentation type: Oral Presentation
Poster number: P33 - **Giusto** Room

Establishing the mechanism underlying the Parkinson disease (PD) risk associated with GBA1 variants has been quite challenging. Both misfolded glucocerebrosidase and accumulated lipid substrate due to reduced enzymatic activity have been considered culprits. To dissect these mechanisms, we generated an iPSC line from a patient with both type 1 Gaucher disease (GBA1: N370S/N370S; p.N409S/p.N409S) and PD and successfully created both reverted wild-type and knockout lines to eliminate misfolded glucocerebrosidase and modulate lipid accumulation. The isogenic iPSC lines were edited to generate high-purity dopaminergic neurons (DANs) and to enable organelle isolation by adding a Lyso-IP tag. The lines were differentiated into dopaminergic neurons, and lysosomal pull-down as well as lipidomic, proteomic and RNAseq studies were performed on each. The wild-type, parental and knockout

DANs appropriately exhibited decreasing glucocerebrosidase levels and progressive accumulation of glucosylceramide and glucosylsphingosine. Strikingly, GPNMB, whose levels correlate with PD risk, was diminished in knockout dopaminergic neurons but elevated in N370S/N370S dopaminergic neurons, revealing a dosage-dependent regulation of GPNMB by lipid storage in disease-relevant neurons. These results associate PD risk levels of GPNMB with lipid perturbations specific to GBA1 variants in disease-vulnerable neurons, a finding further supported by analysis of cerebrospinal fluid (CSF) from patients with PD. Analysis of cerebrospinal fluid (CSF) from PD patients with and without GBA1 variants further confirmed that GBA1 variants lead to increased GPNMB levels, particularly in GD/PD patients. Collectively, our findings, enabled by this unique panel of GBA1 isogenic iPSC lines engineered from a GD/PD donor, implicate lipid-driven modulation of GPNMB as an important mechanism contributing to GBA1-associated pathogenicity in PD. This discovery may also explain the increased PD risk conferred by other mild GBA1 variants. These isogenic lines further provide a broadly applicable platform for drug-discovery efforts targeting GBA1 variants and for genetic screens aimed at identifying factors modulating GCase activity.

Conflict of Interest: None declared.

O16- Mutant microglia from Parkinson's disease patients with heterozygous GBA1 mutations are key determinants of alpha-synuclein aggregation and dopamine neuron pathology

Manoj Kumar[1], Paula A. Rozenfeld[2], and **Ricardo A. Feldman[1]**

[1]Department of Microbiology and Immunology, University of Maryland School of Medicine, Baltimore, MD 21201, United States; [2]Instituto de Estudios Inmunológicos y Fisiopatológicos (IIFP), UNLP, CONICET, asociado CIC PBA, Facultad de Ciencias Exactas, La Plata, Argentina.

Presentation type: Oral Presentation
Poster number: P34 - **Giusto** Room

Background and Hypothesis: Neuroinflammation, particularly microglial activation, is thought to play a critical role in *GBA1*-associated Parkinson's disease (*GBA1*/PD), but the mechanisms involved remain unclear. We hypothesize that *GBA1* mutations drive aberrant microglial activation, and that the resulting inflammatory environment contributes directly to neuronal pathology in *GBA1*/PD.

Experimental system: To test this hypothesis, we examined the effect of iPSC-derived microglia from *GBA1*/PD patients harboring frequent heterozygote mutations (*GBA1*/WT), on a-synuclein aggregation and dopamine (DA) neuron pathology. Our experimental system was co-cultures of DA neurons with patient-derived microglia from identical twins discordant for PD and from other PD patients. Microglial activation was evaluated by morphological analysis, inflammatory cytokine production (TNF-α, IL-1β, IL-6), phagocytic activity, and signaling cascade activation (STING, NLRP3 inflammasome). Neuronal pathology was assessed in microglia/DA neuron co-cultures by quantifying phosphorylated α-synuclein (pS129) and neurofilament light chain (NF-L). Pharmacological interventions included incubation with STING and NLRP3 inhibitors, and with the cytokine-blocking agents UCB-9260, targeting TNF-α, and Anakinra, an antagonist of IL-1β.

Results: The mutant *GBA1* microglia were activated as determined by elevated expression of inflammatory cytokines (TNF-α, IL-1β, IL-6), and NLRP3 and STING. The *GBA1*-activated

microglia induced higher α-synuclein phosphorylation and aggregation in DA neurons, and there was increased NF-L release. Inhibition of STING or NLRP3 reduced inflammatory cytokine production by mutant microglia, while blockage of TNF-α and IL-1β signaling decreased α-synuclein aggregation in DA neurons.

Conclusions: We conclude that mutant *GBA1* microglia are a key determinant of α-synuclein pathology, and that these effects are likely a result of microglia activation caused by mutant *GBA1*. Our findings implicate STING- and NLRP3-dependent pathways, as well as TNF-α and IL-1β signaling, as important mediators of this neuroinflammatory process. Targeting inflammatory microglial pathways may provide a promising therapeutic strategy for arresting disease progression in *GBA1*-associated PD, alone or in combination with other treatments.

Conflict of Interest: None declared.

O17- Utilising machine learning for Gaucher disease: predicting structural defects due to mutation of beta-glucocerebrosidase

Mihaela Atanasova[1], **Thomas J. McCorvie**[1], Brian Marsden[1], Wyatt W. Yue[1]

[1]Newcastle University, United Kingdom

Presentation type: Oral Presentation
Poster number: P35 - **Giusto** Room

Gaucher disease is caused by inherited pathogenic mutations in the GBA gene encoding for the enzyme beta-glucocerebrosidase (GBA). A lysosomal protein, GBA's key role is the metabolism of glycosphingolipids. Hundreds of mutations have been linked to Gaucher disease with the majority resulting in single amino acid changes in the GBA protein however, their molecular effects on protein structure, stability, and function are poorly understood. This limits accurate interpretation and understanding of disease severity and hinders development of rational therapeutics.

As part of the Horizon Europe-funded Recon4IMD consortium aiming to improve the diagnosis and systematic characterisation of IMDs, we are developing a computational and experimental structural biology pipeline to systemically characterise Gaucher disease-associated GBA mutations. This pipeline combines advancements in computational structural biology tools for protein structure prediction, including AlphaFold3, to assess how mutations impact protein folding, stability, and function. These predictions are then compared to experimental data of recombinant GBA mutants including structure determination by cryo-electron microscopy along with enzyme stability and kinetic assays.

Our initial computational analysis indicates a strong correlation between our enzyme structure and stability predictions, and pathogenicity data for several GBA variants spanning a range of disease severity. Preliminary studies on a selection of recombinantly expressed GBA mutants covering pathogenic (p.R131C, p.N370S, p.D409H, p.L444P) and potentially benign (p.E326K, p.D295N) mutants agree with computational predictions. We find that the pathogenic mutants p.D409H and p.L444P result in severe misfolding and no recombinant protein whereas the remaining soluble GBA variants demonstrated lower activity and thermal stability.

Ongoing work will focus on determining the structures of these GBA variants by cryo-electron microscopy to validate the predicted structures. Our method represents a unique approach to

determining the molecular mechanisms of Gaucher linked mutations for improving disease severity interpretation.

Conflict of Interest: None declared.

O18- Novel High-Resolution Exosomal Transcriptomics for Biomarker Discovery in Gaucher Disease

Praveensingh Hajeri[1], Nathan Phan[1], Adam C. Herman[1], Subbaya Subramanian[1], **Reena V. Kartha[1]**

[1]Center for Orphan Drug Research/University of Minnesota, United States

Presentation type: Oral Presentation
Poster number: P36 - **Giusto** Room

Gaucher disease (GD), caused by pathogenic variants in the GBA1 gene, leads to impaired glucocerebrosidase activity and accumulation of glycosphingolipids. This primary defect drives a cascade of secondary cellular abnormalities, including mitochondrial dysfunction, oxidative stress, and chronic inflammation. Lysosomes also play a central role in extracellular vesicle (EV) biogenesis and cargo loading; therefore, lysosomal dysfunction in GD is expected to significantly alter EV RNA composition, positioning EV-derived RNA as a rich and underexplored source of disease biomarkers. The overarching goal of this study was to establish a high-resolution platform to explore EV (primarily exosomal) transcriptomics to accelerate biomarker discovery, disease sub-classification, and development of diagnostic and prognostic assays for GD.

EVs were isolated from patient-derived GD fibroblast lines harboring either mild (N370S/84GG) or severe (L444P/S364T) GBA1 variants, as defined by residual glucocerebrosidase activity, and compared with normal human dermal fibroblasts (NHDF). EVs' RNA cargo was analyzed using our novel, patented next-generation sequencing (NGS) library preparation technology specifically optimized for low-input, fragmented, and all RNA species.

Our platform enabled the detection of an unprecedented number of EV-associated transcripts, yielding at least a threefold increase in unique transcript recovery (≥100,000 transcripts) compared to prior reports. A single, unified workflow robustly captured both small RNAs (including miRNAs) and longer RNA species (mRNAs and lncRNAs). Importantly, we identified more than 1,500 and 3,400 transcripts uniquely associated with mild and severe GD, respectively, including over 105 miRNAs, providing a large, previously inaccessible pool of candidate biomarkers. In addition, extensive transcript coverage across the GBA1 genomic locus was observed, potentially enabling mutation detection without the need for a separate DNA sequencing.

Collectively, these results demonstrate that our high-efficiency NGS technology generates unprecedented data depth and resolution, enabling transformative advances in EV-based biomarker discovery, validation, disease sub-classification, and integrated molecular diagnostics for Gaucher disease.

Funding: Takeda Pharmaceuticals

Conflict of Interest: R.K. has received IIS research grants from Sanofi, Pfizer, Takeda Pharmaceuticals and education grant from Sanofi. All other authors have no COI to disclose.

O19- Comparison of human and zebrafish glucocerebrosidase and generation of chimeric forms: importance of non-catalytic loops for catalytic activity and transglucosylation

Mats J. Bulterman[1], Lindsey T. Lelieveld[1], Mihaela Atanasova[2], Myron N.F. Hensgens[1], Fenna D. Janssen[1], Rolf G. Boot[1], Johannes M.F.G. Aerts[1]

[1]Department of Medical Biochemistry, Leiden Institute of Chemistry, Leiden University, Leiden, The Netherlands; [2]Centre for Medicines Discovery, Nuffield Department of Medicine, University of Oxford, Oxford, United Kingdom

Presentation type: Oral Presentation
Poster number: P37 - **Giusto** Room

Human (hGCase) and zebrafish glucocerebrosidase (zfGCase) are similar: their catalytic pockets are very homologous. Nevertheless, there are striking differences between hGCase and zfGCase, such as broader thermostability of zfGCase, its lower pH-optimum, lack of stimulation by specific detergents, and its inability to generate GlcChol through transglucosylation. GCase has several dynamic loops beyond the catalytic pocket: these are less well conserved. Their roles and importance are largely unknown. Generated were zebrafish-human GCase chimeric enzymes by swapping of loops. Importantly, introducing zfGCase loops into hGCase significantly affected its catalytic properties: particularly introduction of zf-Loop 1 in hGCase increased in vitro activity towards 4MU-Glc and GlcChol. Thus, introducing zfGCase loops into hGCase significantly affected its catalytic properties. Inspired by the above, point mutations in hGCase that increase in vitro hydrolytic activity and transglycosylation capacity were identified: V343A & F347P.

Conflict of Interest: None declared.

Session 5 – Comorbidities in Gaucher Disease

O20- Longitudinal follow-up of GBA1-carriers for prodromal features of Parkinson disease, Sidransky syndrome

Michal Becker-Cohen[1], Ari Zimran[1], Dafna Frydman[1], Elena Shulman[1], Tama Dinur[1], Gilad Yahalom[1], Mikhal Cohen[1], Shoshana Revel-Vilk[1]

[1]Shaare Zedek Medical Center

Presentation type: Oral Presentation
Poster number: P81 - **Zodiaco** Room

Carriers of GBA1 gene variants (GBA1-carriers) have an increased risk of developing Parkinsons disease (PD). Detecting prodromal PD, before the onset of motor symptoms, could allow timely interventions to slow or even prevent disease progression. Over the past nine years, our team at the Gaucher Unit, Shaare Zedek Medical Center, Jerusalem, has conducted systematic screening of GBA1-carriers for early prodromal features of PD using a comprehensive battery of non-invasive assessments, including clinical, cognitive, motor, olfactory, autonomic, and neuroimaging evaluations. Methods: In this longitudinal study, 26 mono- and bi-allelic GBA1-carriers (i.e., patients with Gaucher disease), initially identified with increased echogenicity on transcranial sonography (TCS) and/or olfactory decline, were re-assessed after a median of 5 years (range 1-8). We compared prodromal markers between baseline and follow-up visits at

both the group and individual levels. Results: Group-level comparisons revealed significant changes only in bowel movement frequency ($p = 0.011$) and performance on a color discrimination test ($p = 0.028$). However, individual-level analyses demonstrated considerable heterogeneity, with eight participants showing progression predominantly across imaging, sensory and autonomic function, cognitive performance, and sleep domains. Notably, ten participants exhibited three or more abnormal prodromal features at reassessment; seven of these underwent ^{18}F-FDOPA PET-CT imaging, all of which confirmed dopaminergic dysfunction. Subsequently, two individuals received a clinical diagnosis of PD following their reassessment visit. Conclusions: Although cohort-wide trends were modest, these results underscore the importance of individualized, longitudinal monitoring of GBA1-carriers for early detection of PD progression. As disease-modifying therapies for PD approach clinical availability, such early detection strategies will be critical for selecting patients who may benefit most from timely intervention, ultimately improving outcomes in this high-risk population.

Conflict of Interest: The SZMC Gaucher Unit receives support from Sanofi/Genzyme for participation in the ICGG Registry and from Takeda for the GOS Registry. A.Z. receives honoraria from Takeda, Pfizer, and BioEvents and consultancy fees from Takeda, NLC Pharma, Insightec, and Prevail therapeutics is employed by the company Agyany pharma. S.R.-V., receives grant/research support, honoraria, and advisory fee from Takeda, Pfizer, and Sanofi/Genzyme. All others- none declared.

O21- Mechanisms Underlying Mutant LRRK2's Modifying Effect on GBA1-Associated Parkinson Disease

Vera Serebryany-Piavsky[1], Mia Horowitz[1]

[1]Tel Aviv University, Tel-Aviv, Israel

Presentation type: Oral Presentation
Poster number: P82 - **Zodiaco** Room

Gaucher disease (GD) results from biallelic mutations in the acid beta-glucocerebrosidase (GCase) encoding gene (GBA1). Carriers of GBA1 mutations exhibit a higher propensity to develop Parkinson disease (PD), the second most common neurodegenerative disorder, than the general population. Although most cases are sporadic, in 5-10% of patients PD is caused by mutations in several genes, including GBA1 and LRRK2, both prevalent in the Ashkenazi Jewish population. Clinical studies have suggested that carriers of mutations in both genes exhibit a milder disease phenotype than GBA1 carriers alone, indicating genetic interplay in PD pathogenesis.

To explore this interplay, we used Drosophila to model the effect of mutant LRRK2 (mLRRK2) on GBA1-associated PD. Co-expression of mLRRK2 with mutant GBA1 (mGBA1) improved multiple PD-related phenotypes: it attenuated ER stress and unfolded protein response (UPR) activation, reduced neuroinflammation and dopaminergic neuron loss, enhanced locomotion, and extended survival. These improvements were accompanied by a significant reduction in steady-state levels of mutant GCase (mGCase), implicating mLRRK2 in the enhanced clearance of misfolded, ER-retained enzyme.

Pharmacological and chemical chaperones improved survival in mGBA1 single- but not double-mutant flies, indicating that mLRRK2 and chaperone therapies likely act through overlapping mechanisms to reduce ER-retained mGCase. Proteasomal degradation was unaltered in double mutant flies, whereas altered autophagic markers in double mutants indicate that mLRRK2 promotes autophagic degradation of mGCase.

To test whether mLRRK2 effect on mGCase is general and not GBA1-specific, mLRRK2 was co-expressed with a different lysosomal enzyme, GLA-encoded α-galactosidase A. Similar improvements in PD-related phenotypes were observed.

Collectively, our results indicate that mLRRK2 confers a general protective effect on misfolded, UPR-activating proteins by promoting their autophagic removal and degradation, thereby mitigating ER stress associated with retained mutant lysosomal enzymes.

Conflict of Interest: None declared.

O22- Non-Motor and Neuropsychological Differences Across the GBA1 Spectrum

Yonatan Serlin[1], Samantha Nishimura[1], Emory Ryan[1], Grisel Lopez[1], **Ellen Sidransky[1]**

[1]National Institutes of Health, Unites States

Presentation type: Oral Presentation
Poster number: P83 - **Zodiaco** Room

Background: Tracking non-motor symptoms (NMS) and neuropsychological function provides valuable tools for assessing progression in neurodegenerative diseases. This study aimed to characterize differences between individuals with Gaucher disease (GD), carriers of GBA1 variants (GC), and GBA1-associated Parkinson disease (GBA-PD). A key objective was to explore whether markers observed in GBA-PD could serve as potential early indicators of disease conversion in GD or GC.

Methods: 123 participants (GD: n=58, GC: n=36, GBA-PD: n=29) enrolled at the NIH between 2005 and 2023 were analyzed. The Wechsler Adult Intelligence Scale (WAIS) was performed to derive Full Scale, Performance, and Verbal Intelligence Quotients (FSIQ, PIQ, VIQ). NMS were assessed using the Non-Motor Symptoms Questionnaire (NMSQ), Beck Depression Inventory (BDI), Fatigue Severity Scale (FSS), and Epworth Sleepiness Scale (ESS). Olfaction was measured using the University of Pennsylvania Smell Identification Test (UPSIT). Longitudinal data was available from 79 participants over a 12-year period.

Results: Cross-sectionally, GBA-PD participants reported a significantly greater NMS burden (mean NMSQ score 10.3) compared to GD (4.5) and GC (3.8) groups ($p<0.001$). This burden was significantly greater across eight NMSQ subdomains ($p<0.05$ for all eight). GBA-PD scored higher on the ESS for daytime sleepiness ($p<0.05$), while FSIQ/VIQ showed no group differences. Longitudinally, GBA-PD patients exhibited increasing NMS burden and olfactory decline, while most GD and GC participants remained stable.

Discussion: GBA-PD participants exhibited worsening across most NMSQ subdomains, corroborated by sleepiness and fatigue measures, consistent with a multisystem disease. In contrast, attention/memory and overall IQ measures were less informative. The low PD prevalence and lack of true “converters” in this longitudinal study demonstrate that assessing the impact of an early intervention trial will be very challenging. Longitudinal studies are necessary to assess the predictive capacity of NMSQ subdomains and olfactory decline to aid in early stratification and risk assessment for disease conversion.

Conflict of Interest: None declared.

O23- Not All ‘Mild’ Genotypes Are Equal: Divergent Skeletal Burden in c.[1226A>G] Homozygous versus c.[1226A>G]/Mild Gaucher Disease

Irene Serrano-Gonzalo[1], Isidro Arévalo-Vargas[1], Sonia Roca-Esteve[1], Carlos Lahoz Gil[1], Esther Valero-Tena[1], Mercedes Roca-Espiau[1], Marcio Andrade-Campos[1], Pilar Giraldo[1]

[1]Fundación Española para el Estudio y Terapéutica de la Enfermedad de Gaucher

Presentation type: Oral Presentation
Poster number: P84 - **Zodiaco** Room

Skeletal involvement is the main driver of long-term morbidity in Gaucher disease type 1 (GD1). Although the c.[1226A>G] (N370S) variant is classically associated with a mild phenotype, bone disease remains highly heterogeneous, even among genotypes considered “mild”. Direct comparisons between N370S homozygotes and N370S/mild compound heterozygotes are limited.

We conducted a retrospective study using the Spanish Gaucher Disease Registry to compare skeletal disease at diagnosis in GD1 patients homozygous for c.[1226A>G] versus c.[1226A>G]/mild genotypes, and to identify potential clinical and biochemical modifiers. Genotypes were classified as c.[1226A>G];c.[1226A>G] or c.[1226A>G]/mild, with “mild” defined by functional severity. Skeletal involvement was assessed by the Spanish MRI scale (S-MRI), bone crises, osteonecrosis, vertebral deformities, and DXA Z-scores. Biomarkers (Lyso-Gb1, chitotriosidase), hematological, and visceral parameters were recorded. Analyses were adjusted for age, sex, splenectomy, and treatment exposure.

Among 436 GD1 patients, 56 were c.[1226A>G] homozygous and 39 c.[1226A>G]/mild. Clinically relevant skeletal disease (S-MRI ≥11) affected half of c.[1226A>G]/mild patients versus one third of homozygotes. Lyso-Gb1 levels were over twice as high in c.[1226A>G]/mild patients (median 98.3 vs 44.8 ng/mL), indicating higher metabolic burden. Osteonecrosis prevalence was similar (10.7% vs 10.2%), while bone crises were slightly less frequent in homozygotes (5.5% vs 7.1%). Osteopenia/osteoporosis at diagnosis was low and comparable (13.3% vs 17.9%). Visceral and hematological parameters did not differ. After ~20 years of follow-up, new bone crises and joint replacement were rare and similar between groups.

Despite being considered “mild,” c.[1226A>G] homozygotes exhibit a more favorable skeletal profile than c.[1226A>G]/mild patients. These results highlight the dissociation between visceral and skeletal disease in GD1 and support the need for genotype-informed, individualized skeletal monitoring, even in clinically mild cases.

Conflict of Interest: P.G., received research grants from Sanofi and Takeda. All other authors declare no conflicts of interest.

O24- The "Perfect Storm" of Wnt Inhibitors Drives Early Osteoporosis in Female Patients with Gaucher Disease

Margarita M Ivanova[1], Julia Dao[1], and Ozlem Goker-Alpan[1]

[1]Lysosomal and Rare Disorders Research and Treatment Center

Presentation type: Oral Presentation
Poster number: P85 - **Zodiaco** Room

Background: Gaucher disease (GD) results from glucocerebrosidase enzyme deficiency, leading to glycosylceramide and glucosylsphingosine accumulation, triggering an immune response with chronic inflammation that transforms macrophages into Gaucher cells. This

disrupts bone marrow homeostasis and remodelling, leading to skeletal complications like bone marrow infiltration, Erlenmeyer flask deformities, and decreased bone mineral density (BMD). Female GD patients experience earlier and more frequent osteoporosis and fractures, suggesting an interplay of GD-specific pathophysiology and estrogen-related factors. The Wnt/β-catenin pathway drives osteoblast-mediated bone formation. Wnt-inhibitors (sclerostin, DKK1/2, SFRP1) disrupt bone remodelling by suppressing osteoblast activity while resorption persists, causing BMD loss and osteoporosis.

Purpose: To investigate the role of Wnt/β-catenin pathway inhibition in early osteoporosis among female GD patients, focusing on Wnt inhibitors and their modulation by inflammation, bone marrow architecture, and hormonal influences.

Methods: Serum levels of sclerostin, DKK1, DKK2, and SFRP1 were measured via enzyme-linked immunosorbent assays in 30 female GD patients, categorized by BMD status (normal, osteopenia, osteoporosis) and menopausal status, and compared to 22 healthy female controls.

Results: Sclerostin, DKK1, and DKK2 levels were elevated in GD patients compared to controls. Sclerostin increased significantly with age, correlating with bone pain and marrow infiltration. DKK1 was notably elevated in premenopausal females with osteopenia, indicating early osteoblast suppression, potentially influenced by estrogen. Conversely, DKK2 levels rose in postmenopausal females with declining BMD, suggesting a role after age 55. SFRP1 levels decreased in osteoporotic patients, possibly reflecting a compensatory attempt to enhance Wnt/β-catenin signalling.

Conclusions: The synergistic upregulation of sclerostin, DKK1, and DKK2 creates a “perfect storm”; of Wnt/β-catenin pathway inhibition, suppressing osteoblast activity and accelerating BMD loss in female GD patients. This effect, amplified by GD-specific inflammation and postmenopausal estrogen decline, underscores a novel mechanism for early osteoporosis and highlights Wnt pathway components as potential therapeutic targets to mitigate bone disease progression.

Funding: Investigator-Initiated funding from Takeda, IISR-2023-200357

Conflict of Interest: None declared.

Session 6 – Rapid Communications

O25- Expression of Mild GBA1 Mutations in a Fly Model

Aparna Kuppuramalingam[1], Vera Serebryany-Piavsky[1] and Mia Horowitz[1]

[1]Tel Aviv University, Tel-Aviv, Israel

Presentation type: Rapid Communication
Poster number: P28 - **Giusto** Room

Biallelic mutations in the GBA1 gene lead to Gaucher disease (GD). We have previously shown that the severe L444P mutation and the milder N370S mutation are recognized as misfolded in the ER, resulting in their retention, ER-associated degradation (ERAD), and activation of the Unfolded Protein Response (UPR). UPR can be alleviated by chemical or pharmacological chaperones-small molecules capable of crossing the blood-brain-barrier, that promote the exit

of mutant proteins from the ER, allowing their trafficking to lysosomes. Monoallelic mutations in the GBA1 gene are a predisposing factor for the development of Parkinson disease (PD).

We have documented the use of Drosophila melanogaster as a platform to study UPR induced by human mutant GBA1 variants, which lead to the death of dopaminergic cells and the development of parkinsonian signs, and to test chaperones for their ability to reduce ER stress. In the present study, we investigated the ability of the mild R496H GBA1 mutation and the very mild E326K mutation, to induce parkinsonian signs when expressed in the fly dopaminergic neurons. Both mutations are linked to GBA1-associated PD.

Interestingly, expression of the R496H and the E326K mutations, caused ER retention of the mutant proteins and triggered UPR and neuroinflammation in the flies. However, these cellular pathologies were insufficient to trigger the development of parkinsonian signs in flies expressing them, suggesting that misfolding must surpass a threshold to elicit such manifestations in this model.

Conflict of Interest: None declared.

O26- Accelerating GD Diagnosis and Enabling Reliability differential detection with ASMD, thanks to MSMS analysis

Magali Pettazzoni[1], Rivaux Antoine[1], Guffon Nathalie[1], Fouilhoux Alain[1], Brassier Anaïs[1], Guerin François[1], Pasquier Laurent[1], Sekkach Youssef[1], Froissart Roseline[1]

[1]Hospices Civils De Lyon

Presentation type: Rapid Communication
Poster number: P29 - **Giusto** Room

Introduction: Tandem mass spectrometry (MS/MS) using dried blood spots (DBS) has become a robust and practical approach to newborn screening and the diagnosis of lysosomal disorders. The aim of our study was to evaluate the performance of MSMS analysis on DBS for the diagnosis of Gaucher disease (GD).

Methods/Results: Over six years, 37,000 DBS samples were analyzed using an MS/MS kit which allows the measurement of six lysosomal enzymes in multiplex, including β-glucocerebrosidase (ABG) for GD and acid sphingomyelinase (ASM) for ASM deficiency, two diseases that share clinical symptoms. Alpha-L-iduronidase (IDUA) was used as a control enzyme. Of the DBS samples received, 13.7% (n=5,112) were addressed for suspected GD and/or ASMD. In control subjects, ABG activity exhibited a broad spectrum of values, with a median of 5.56 µmol/L/h (SD 4.04). The cut-off value was defined as the 5th percentile (3.70 µmol/L/h). We identified 56 GD patients (diagnosis rate: 1.24%), consistently displaying markedly decreased ABG activity in DBS, with a median of 0.33 µmol/L/h (range 0.01–1.13), associated with a low ABG/IDUA ratio. There was no correlation of activity with age at diagnosis (median 26 years; 22 pediatric and 34 adult cases). Heterozygous carriers (n = 14) displayed intermediate activities with a median of 2.14 µmol/L/h (range 1.37–2.98), significantly higher than in patients ($p < 0.05$), but lower than in the control group ($p < 0.0001$). We identified 50 ASMD patients (diagnosis rate: 3.3%). Interestingly, six ASMD patients (12% of ASMD cases) were incidentally detected during Gaucher testing thanks to the multiplex MS/MS approach.

Conclusion: DBS-based multiplex MS/MS represents a powerful front-line diagnostic tool for GD when integrated into a multimodal process combining biochemistry, molecular genetics

and clinical expertise. This approach simultaneously improves ASMD detection rates and reduces diagnostic delay through multiplex enzymatic screening.

Conflict of Interest: None declared.

O27- The platelets lipidomic signature in Gaucher Disease

Giuseppe Uras[1,2]; Veronica Lentini[2]; Antonella Pantaleo[2]; Pierluigi Caboni[3]; Cristina Manis[3]; David Moreno Martinez[1], Derralynn Hughes[1]

[1]Department of Haematology, UCL Cancer Institute, London, United Kingdom; [2]Department of Biomedical Science, University of Sassari, Viale San Pietro, Sassari, Italy; [3]Department of Chemistry, University of Cagliari, Piazza d'Armi, Cagliari, Italy

Presentation type: Rapid Communication
Poster number: P30 - **Giusto** Room

Gaucher disease (GD) arises from biallelic GBA1 mutations, impairing lysosomal glucocerebrosidase (GCase) activity and leading to glucosylceramide (GlcCer) and glucosylsphingosine (GlcSph) accumulation. While glycosphingolipid storage dominates GD lipid pathology, broader membrane lipid dysregulation in peripheral cells like platelets remains underexplored. This study employed untargeted and targeted lipidomics via high-resolution mass spectrometry on platelet samples from GD patients, heterozygous GBA1 mutation carriers, and healthy controls to uncover comprehensive lipid profiles.

Multivariate analyses, including principal component analysis (PCA) and partial least squares-discriminant analysis (PLS-DA), revealed a robust platelet lipidomic signature distinguishing GD from carriers and controls. Phospholipid species—particularly phosphatidylcholine (PC), phosphatidylethanolamine (PE), and lysophospholipids—emerged as primary drivers of group separation, explaining greater variance than GlcCer or GlcSph elevations. Targeted quantification confirmed elevated PC/lysophosphatidylcholine (LPC) ratios and PE alterations in GD, indicative of membrane remodeling and phospholipase dysregulation beyond canonical storage defects.

These phospholipid-centric changes highlight GBA1 deficiency's systemic impact on lipid metabolism, extending to platelet membrane homeostasis and potentially contributing to thrombocytopenia observed in GD. Unlike prior plasma-focused studies emphasizing secondary glycolipid shifts, platelet-specific profiling underscores phospholipids as key discriminatory features.

This lipidomic framework redefines GD platelet pathology, prioritizing phospholipid biomarkers for disease monitoring and therapeutic stratification. Future validation could link these signatures to GCase pharmacochaperones or substrate reduction therapies targeting broader lipid pathways.

Conflict of Interest: None declared.

O28- Cellular context matters: strengths and limitations of a GBA1-knockout model for functional assessment of GBA1 variants

Maximiliano E. Ormazabal[1], Eleonora Pavan[1], Emma Cuttini[1], Silvia Cattarossi[1], Natascha Bergamin[1], Mauricio Scarpa[1], Andrea Dardis[1]

Regional Coordinator Centre for Rare Diseases, Academic University Hospital of Udine (ASUFC), Italy

Presentation type: Rapid Communication
Poster number: P31 - **Giusto** Room

Background: Cell-based functional assays are essential tools to assess the impact of GBA1 variants on glucocerebrosidase (GCase) activity and the reclassification of variants of uncertain significance within a controlled cellular environment. However, the biological relevance of these systems depends strongly on the cellular context and expression strategy. We developed and evaluated a cell-based assay to study GCase function under near-physiological expression conditions.

Methods: A HEK293 GBA1 knockout (GBA_KO) cell line was generated using CRISPR/Cas9 technology to abolish endogenous GCase expression. An expression vector (pAC-GBA1), bearing wild-type and selected benign or pathogenic variants driven by the constitutive pGK promoter, was designed to achieve physiologically levels of GCase expression and minimize overexpression-related artifacts. The constructs were transiently transfected into GBA_KO cells. GCase activity was quantified, and protein maturation/intracellular trafficking was evaluated by Endo-H digestion.

Results: In this system. cells expressing a benign variant exhibited GCase activity comparable to wild-type, whereas pathogenic variants showed reduced enzymatic activity. In contrast to GCase activity profiles observed in patient-derived fibroblasts, residual GCase activity was higher in of cells expressing the L444P variant than in cells expressing N370S. Furthermore, Endo-H digestion revealed an immature glycosylation profile of all exogenously expressed GCase variants, consistent with endoplasmic reticulum retention. This maturation pattern did not recapitulate the profiles observed in patient-derived cells.

Conclusions: Cellular knockout models represent valuable tools for investigating specific aspects of Gaucher disease. However, in the context of exogenous and transient expression of certain GBA1 variants, discrepancies in enzymatic activity and protein maturation may arise. Our findings highlight the need for careful interpretation of functional data generated in cell-based systems, as the choice of cellular model and expression strategy influences functional readouts. Therefore, functional studies should therefore be interpreted within the limitations of each model and, whenever possible, complemented by data from patient-derived cells or alternative experimental systems.

Conflict of Interest: None declared.

O29- Parkinson's disease and dementia with Lewy bodies in Gaucher disease: a multicenter longitudinal study

Marco Percetti[1,2], Edoardo Monfrini[1,2], Emanuele Frattini[1,2], Giulia Franco[1,2], Ilaria Trezzi[1,2], Maria Chiara Malaguti[3], Francesco Cavallieri[4], Franco Valzania[4], Giovanni Cossu[5], Silvia Ramat[6], Alessandra Govoni[6], Cristoforo Comi[7], Alessandro Tessitore[8], Rosa De Micco[8], Antonio Barbato[9], Paolo Tirelli[10], Francesca Spagnolo[11], Maria Domenica Cappellini[12], Elena Cassinerio[12], Irene Motta[12], Natalia Scaramellini[12], Francesca Carubbi[13], Fabio Nascimbeni[14], Lorenza Borin[15], Emanuele Cerulli[16], Fiorina Giona[16], Francesca Leo[17], Massimo Marano[17,18], Alessio Barnaba Di Fonzo[1,2]

[1]Dino Ferrari Center, Neuroscience Section, Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy; [2]Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Neurology Unit, Milan, Italy; [3]Dipartimento di Scienze Neurologiche, Ospedale Santa Chiara, Trento, Italy; [4]Neurology

Unit, Neuromotor & Rehabilitation Department, Azienda USL-IRCCS di Reggio Emilia, 42123 Reggio Emilia, Italy; [5]Neurology Service and Stroke Unit, Department of Neuroscience, AO Brotzu, Cagliari, Italy; [6]Parkinson Unit, Neuromuscular-Skeletal and Sensory Organs Department, AOU Careggi, Florence, Italy; [7]Neurology Unit, S. Andrea Hospital, Department of Translational Medicine, University of Piemonte Orientale, 13100 Vercelli, Italy; [8]Department of Advanced Medical and Surgical Sciences, University of Campania "Luigi Vanvitelli", Naples, Italy; [9]Department of Clinical Medicine and Surgery, "Federico II" University Hospital, Naples, Italy; [10]UOC Medicina Generale, Ospedale del Mare ASL Na 1, Naples, Italy; [11]Neurological Department, Antonio Perrino's Hospital, Brindisi, Italy;[12]Unit of Internal Medicine, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; [13]U.O.C. Medicina metabolica AOU Modena, Metabolic Medicine Unit, Modena University Hospital, Modena, Italy; [14]Regional Referral Centre for Lysosomal Storage Diseases, Division of Internal Medicine and Metabolism, University Hospital of Baggiovara, AOU of Modena, Modena, Italy; [15]Department of Hematology, Asst Monza, San Gerardo Hospital, 20900 Monza, Italy; [16]Department of Translational and Precision Medicine, Sapienza University, Rome, Italy; [17]Unit of Neurology, Neurophysiology, Neurobiology and Psychiatry, Department of Medicine, University Campus Bio-Medico of Rome, Rome, Italy; [18]Fondazione Policlinico Universitario Campus Bio-Medico, Rome, Italy.

Presentation type: Rapid Communication
Poster number: P88 - **Zodiaco** Room

Background: Gaucher disease (GD) is a lysosomal storage disorder caused by biallelic GBA1 variants, which represent the most common genetic risk factor for Parkinson's disease (PD) and dementia with Lewy bodies (DLB).

Objectives: To investigate the occurrence of PD and DLB in a cohort of type 1 and type 3 GD patients (GD1, GD3), and to identify possible predictors of PD or DLB phenoconversion in these patients.

Methods: GD patients from multiple centers were consecutively evaluated by neurologists with expertise in movement disorders at two different time-points (T0, at baseline; T1, after 4±2y).

Results: One-hundred-thirty-six GD1 and 13 GD3 patients were evaluated at T0 (mean age-at-T0 47.6±15.6y). The mild N409S variant in compound heterozygosity with another GBA1 variant (N409S/other) was the most frequent genotype (72.1%). Diagnosis of PD and DLB was reached in 18 (13.2%) and two (1.5%) GD1 patients, respectively. Fifty-four GD1 and five GD3 patients were re-evaluated at T1. PD and DLB phenoconversion were observed in four (7.4%) and seven (13%) GD1 patients, respectively. Two (15.4%) GD3 patients developed PD. PD diagnosis preceded that of GD in six (4.4%) GD1 patients. The lifetime risk to develop PD was 25.5% in N409S/other GD1 patients and 0% in homozygous N409S patients at 60y (p = 0.003), 34.8% and 33.3% respectively at 70y (p = 0.54).

Conclusions: This study highlights the potential of close follow-up of GD patients to identify possible predictors of phenoconversion to PD or DLB.

Conflict of Interest: None declared.

O30- Severe Secondary GM1 Ganglioside Accumulation in Gaucher Patients' Cell Lines

Rodolfo Tonin[1], Federica Feo[1], Marina Rinaldi[1], Francesca Clemente[1], Costanza Ceni[1], Francesca Cardona[1], Martino Calamai[1], Amelia Morrone[1]

[1]Laboratory of Molecular Genetics of Neurometabolic Diseases Department of Neuroscience and Medical Genetics, Meyer Children's Hospital IRCCS, Florence, Italy

Presentation type: Rapid Communication
Poster number: P32 - **Giusto** Room

Gaucher disease (GD) is a rare genetic metabolic disorder caused by mutations in the GBA1 gene, leading to deficient lysosomal glucocerebrosidase (GCase) activity and the resulting cellular accumulation of glucosylceramide (GlcCer). While primary GlcCer accumulation is the focus of most research, the role of secondary storage materials and their pathological intertwining remains poorly understood, especially in neuronopathic forms of GD.

Using a novel approach based on flow cytometry and fluorescent labelling, we monitored changes in storage materials directly in fibroblasts and neural precursor cells (NPCs) derived from GD patients carrying Asp409Ser/RecNciI and homozygous Leu483Pro mutations, comparing them to wild-type cells.

In Leu483Pro cell lines, we detected primary accumulation of GlcCer alongside a considerable secondary increase in GM1 ganglioside storage, reaching levels comparable to those observed in infantile GM1 gangliosidosis. We then tested the ability of a trivalent trihydroxypiperidine iminosugar compound (CV82), previously shown to act as a pharmacological chaperone for GCase, to reduce these storage materials in fibroblasts and NPCs.

The treatment with CV82 led to a significant reduction in GM1 accumulation only in Leu483Pro cell lines, without significantly affecting GlcCer levels.

Interestingly, CV82 showed no direct action on β-galactosidase, the enzyme responsible for GM1 catabolism, suggesting that the decreasing of GM1 is likely related to as-yet-unknown downstream mechanisms following CV82's primary action on GCase.

In conclusion, this work indicates that tracking secondary storage materials, such as GM1 ganglioside and α-synuclein, in fibroblasts and NPCs can be a key step toward a better understanding of the pathways underlying the severity of neuronopathic GD, highlighting the significance of developing therapeutics capable of reducing both primary and secondary storage accumulations.

Acknowledgments: AMMeC ONLUS; PRIN Bando 2022 Prot.20228S5LWY

Conflict of Interest: None declared.

Session 7 – Therapies in Gaucher Disease

O31- Therapeutic efficacy of a novel glucocerebrosidase variant in a new preclinical model of neuronopathic Gaucher disease

Allan Feng[1], Luisa N. Pimentel Vera[1], Pasqualina Colella[1], Gjalt W. Huisman[2], Victoria Wong[2], Natalia Gomez-Ospina[1]

[1]Department of Pediatrics, Stanford University School of Medicine, Stanford, Unites States; [2]Embold Therapeutics, Inc., Redwood City, Unites States

Presentation type: Oral Presentation
Poster number: P43 - **Giusto** Room

Neuronopathic forms of Gaucher Disease (GD), Types 2 and 3, display the most severe manifestations of GD and currently lack effective treatments. Evaluating any therapeutic modality requires an animal model that mirrors symptoms observed in patients. However,

attempts to create neuronopathic GD mouse models have resulted in mice that succumb too quickly or do not display neuronal-specific phenotypes.

To overcome this limitation, we developed the Thy1-Gba1 knockout mouse—a tamoxifen-inducible, neuron-specific knockout on a D409V mutant background. This model recapitulates key features of neuronopathic GD, including progressive motor impairment, autonomic instability, and neuropsychiatric dysfunction. Thy1-Gba KO mice displayed a median survival of approximately four weeks post-induction, a window that supports longitudinal assessment and therapeutic testing.

We assessed the therapeutic potential of several AAV9 vectors encoding either wild-type glucocerebrosidase (GCase) or an engineered GCase variant that was optimized for half-life in serum, cerebrospinal fluid, lysosomes, and for cellular uptake. Importantly, the AAV9-mediated therapy was delivered systemically at a moderate dose of 2x1013 vg/kg. Thy1-Gba KO mice treated with AAV9 encoding the engineered GCase variant demonstrated normalized motor function, near-complete behavioral recovery, improved growth, and normal survival of up to four months post-tamoxifen. In contrast, the AAV9 encoding wild-type GCase failed to rescue these phenotypes, underscoring its limited efficacy in the CNS.

These findings suggest that the Thy1-Gba KO model replicates important features of neuronopathic GD, offering a viable platform for testing CNS-targeted therapies. Furthermore, our engineered GCase is superior to the wild-type enzyme in rescuing the neuronal phenotype even when delivered systemically at a moderate dose.

Conflict of Interest: G.H., is the CEO of Embold Therapeutics. V.W., is a scientist at Embold Therapeutics. All remaining authors report no conflicts of interest.

O32- A Phase 1 First-in-Human, Single- and Multiple- Ascending Dose Study of Glucosylceramide Synthase (GCS) Inhibitor YH35995 in Healthy Adult Male Participants

Anhye Kim[1], Hyounggyoon Yoo[1], Wonsuk Shin[1], YuKyung Kim[2], Min Young Park[2], Sujin Hyun[2], Eunhye Lee[2], Bomin Kim[2], Jaeyeon Lee[2], Heewon Han[2], Min Jeong Kim[2], Sungjae Lee[2], Jeeyeon Kim[2], Seung-yub Shin[3], Jong Suk Park[3]

[1]Department of Clinical Pharmacology and Therapeutics, CHA University Bundang Medical Center, Seongnam-si, Gyeonggido, Republic of Korea; [2]Clinical and Medical Development Division, R&D, Yuhan Corporation, Seoul, Republic of Korea; [3]R&D Institute, R&D, Yuhan Corporation, Yongin, Republic of Korea

Presentation type: Oral Presentation
Poster number: P44 - **Giusto** Room

Gaucher disease (GD) is a rare, inherited metabolic disorder caused by GBA1 gene mutations, leading to a deficiency of the lysosomal enzyme glucocerebrosidase. This results in the harmful accumulation of glucosylceramide (GL1) in multiple organs. While several types of GD exist, neuropathic forms (types 2 and 3) are more severe, presenting significant central nervous system manifestations. Current therapies cannot effectively cross the blood-brain barrier (BBB), highlighting a critical unmet medical need for novel therapeutics that can efficiently access the brain.

YH35995 is a novel, highly potent, and BBB-penetrating glucosylceramide synthase (GCS) inhibitor. In preclinical studies with a mouse model, oral treatment with YH35995 significantly

reduced GL1 levels in both plasma and brain, improved behavioral abnormalities, and suppressed gliosis. These findings provide a well-founded rationale for the clinical investigation of YH35995.

This First in Human Phase 1, single and multiple ascending dose (SAD/MAD) study (NCT06517914) aims to evaluate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of YH35995 in healthy adult male participants. The SAD part is planned with 5 dose cohorts (3, 10, 30, 60, and 120 mg), with each cohort enrolling 10 participants randomized at a 4:1 ratio (YH35995 : placebo). The MAD part will be conducted with 3 dose cohorts, determined based on the SAD results. Each MAD cohort will enroll 12 participants randomized at a 3:1 ratio (YH35995 : placebo). Particularly the MAD part will include GL1 evaluation in cerebrospinal fluid (CSF) before and after administration. The SAD results and details on the dose cohorts of the MAD will be available in the presentation during the conference, with the MAD anticipated to commence around the end of 2025. The overall results of this study are expected to provide key insights into the safety, dose-response relationship, PK/PD relationship, and the potential dosing regimen of YH35995.

Conflict of Interest: A.H. Kim, H.G. Yoo, and W.S. Shin are investigators which are receiving funding from Yuhan Corporation for conducting the clinical study (YH35995-101). Y.K. Kim, M.Y. Park, S.J. Hyun, E.H. Lee, B.M. Kim, J.Y. Lee, H.W. Han, M.J. Kim, S.J. Lee, J.Y. Kim, S.Y. Shin, J.S. Park are employees of Yuhan Corporation, which is developing YH35995.

O33- Two-year follow up of avigbagene parvec (FLT201) investigational AAV gene therapy in adults with Gaucher Disease type 1: Results from GALILEO-1 and GALILEO-2

Ida Schwartz[1], Ozlem Goker-Alpan[2], Reena Sharma[3], Pilar Giraldo[4], Pamela Foulds[5], Philip Yin[5], Dan Wolf[5], Simon Flynn[5]

[1]Hospital de Clinicas de Porto Alegre, Brazil; [2]Lysosomal and Rare Disorders Treatment Center, Virginia, United States; [3]Salford Royal Hospital, United Kingdom; [4]Hospital Universitario Quironsalud, Zaragoza, Spain; [5]Spur Therapeutics, Stevenage, United Kingdom

Presentation type: Oral Presentation
Poster number: P45 - **Giusto** Room

Avigbagene parvec (FLT201) is an investigational AAV gene therapy for Gaucher disease type 1 (GD1). It comprises a proprietary, liver-tropic capsid (AAVS3), with a unique transgene encoding GCase85, a novel engineered variant of β-glucocerebrosidase (GCase) under control of a liver-specific promoter. GCase85 has improved stability over human GCase by approximately six-fold in serum and 20-fold at lysosomal pH. A single infusion of FLT201 has the potential to deliver continuous, durable endogenous expression of GCase85 eliminating the need for chronic treatment with ERT or SRT. The increased stability of GCase85 provides sustained GCase exposure beyond what is achievable with ERT, leading to increased tissue uptake, which could be important for improved treatment outcomes.

GALILEO-1, the first-in-human trial of FLT201, enrolled six adults with GD1 on stable treatment with either ERT or SRT for at least two years prior to enrollment. Previous treatment duration ranged from between four to twenty-four years. All six participants received a single IV infusion of FLT201 at a low dose of 4.5 x 1011 vg/kg and follow-up duration ranges from 22 to 31 months. All patients are in the long-term follow-up study, GALILEO-2.

Four participants discontinued ERT/SRT following FLT201 administration and remain off their background therapy. In these participants, FLT201 provided durable long-term GCase85 expression with cross-correction of peripheral blood leukocytes. Maintenance or improvement of hemoglobin and platelet count, stability in liver and spleen volumes, and clearance of lyso Gb1 has been sustained or further reduced. Improvements were seen in all four patients in one or more efficacy assessments.

All participants tolerated FLT201 administration well with no infusion-related reactions reported. The overall safety profile of FLT201 was favorable, with no treatment-related serious adverse events and only mild (<2xULN) transient ALT elevations considered related to therapy observed with no impact on efficacy.

Conflict of Interest: I.S. has received honoraria for speaking and travel support from Sanofi and Takeda. O.G-A. has received honoraria for advisory board participation from Spur, Prevail/Lilly and Sanofi; honoraria for speaking and research support from Sanofi. R.S. has received honoraria for consulting from Amicus, Sanofi, Chiesi, Ultragenyx, Immedica and Takeda. P.F., D.W., and S.F. are employees of Spur Therapeutics. P.Y. is a former employee of Spur Therapeutics.

O34- The PROCEED Study: A Phase 1/2 Dose-Escalation Investigation of Systemic AAV9-Based Gene Therapy for Peripheral Manifestations of Gaucher Disease

Ozlem Goker-Alpan[1], Mia Weaver[2], Pilar Giraldo[3], Jennifer L. Cohen[4], Eugen Mengel[5], Jeff Booth[2], Sebastian Boland[2], Rachel Manthe-Gross[2], Daniel Alexander Hatch[2], Sarah Neuhaus[2], Aaron Tward[2]

[1]Lysosomal Rare Disorders Research and Treatment Center, Fairfax, United States; [2]Eli Lilly and Company, Indianapolis, United States; [3]Fundación para el Estudio y la Terapéutica de la Enfermedad de Gaucher y Otras Lisosomales (FEETEG), Zaragoza, Spain; [4]Division of Medical Genetics, Department of Pediatrics, Duke University, Durham, United States; [5]SphinCS GmbH, Institute of Clinical Science for LSD, Hochheim, Germany

Presentation type: Oral Presentation
Poster number: P46 - **Giusto** Room

Background: Gaucher disease (GD) is a rare glycosphingolipid metabolism disorder resulting from a deficiency in the lysosomal enzyme glucocerebrosidase (GCase), which is encoded by the GBA1 gene. Bi-allelic variations in GBA1 lead to the accumulation of glycosphingolipids, particularly the toxic substrate, glucosylsphingosine. GD commonly presents in early adulthood with hepatosplenomegaly, anemia, and thrombocytopenia, while additional complications may include osteopenia, skeletal abnormalities, and pulmonary infiltrates. Enzyme replacement therapy (ERT) and substrate reduction therapy (SRT) may not fully address all peripheral symptoms, and ERT is notably burdensome for many patients. A gene therapy strategy that introduces a functional gene to enable consistent and sustained expression of the deficient protein represents a promising, long-term therapeutic alternative.

Aims: The PROCEED trial is an open-label, Phase 1/2, multicenter, dose-finding clinical study designed to assess the safety and efficacy of LY3884961—a systemically administered rAAV9-GBA1 gene therapy construct—in individuals with peripheral manifestations of GD. Up to 15 adults aged 18 years or older with bi-allelic GBA1 mutations will receive a single intravenous dose of LY3884961 allocated across three sequential escalating cohorts. Low- and mid-dose cohorts have completed enrolment. The primary endpoint is the safety and tolerability of LY3884961. Secondary and exploratory objectives encompass the time to discontinuation and

re-initiation of ERT/SRT as clinically indicated, as well as changes from baseline in platelet count, spleen and liver volumes, bone marrow involvement, bone mineral density, lung function, and pharmacodynamic biomarkers including GCase activity and glycolipids.

Results: The PROCEED trial (NCT05487599) aims to determine whether a single intravenous administration of LY3884961 can safely maintain or improve peripheral clinical parameters of GD following cessation of conventional therapy. Preliminary clinical and biomarker data indicate that LY3884961 is safe, well-tolerated, and holds promise as a potential one-time treatment for Gaucher disease Type 1.

Conclusions: Enrolment in PROCEED remains active; further updates will be provided.

Conflict of Interest: M.W., J.B., S.B., R.M-G., D.A.H., S.N. are employees of Eli Lilly and Company

---

O35- Dose Spacing in Enzyme Replacement Therapy for Stable Type 1 Gaucher Disease: A Non- Inferiority Sequential Trial Emulation from the French Gaucher Disease Registry

Maxime Beydon, Jérôme Stirnemann, Karima Yousfi, Samira Zebiche, Dalil Hamroun, Anaïs Brassier, Samia Pichard, Laure Swiader, Thierry Billette de Villemeur, Bénédicte Héron, Florence Dalbies, Bérengère Cador, Anne-Sophie Guemann, Francis Gaches, Bénédicte Hivert, Vanessa Leguy-Seguin, Agathe Masseau, Yves-Marie Pers, Magali Pettazzoni, Soumeya Bekri, Catherine Caillaud, Edouard Le Guillou, Marie Szymanowski, Leonardo Astudillo, Wladimir Mauhin, Yann Nadjar, Christine Serratrice, Marc G. Berger, Fabrice Camou, Nadia Belmatoug, **Yann Nguyen**

Université Paris Cité

Presentation type: Oral Presentation
Poster number: P47 - **Giusto** Room

Objective: To compare the efficacy and safety of extended interval of enzyme replacement therapy (Q3–4W) versus standard biweekly ERT (QW) in clinically stable type Gaucher disease (GD) patients.

Methods: We emulated a target trial with a sequential trial design, using data from the French Gaucher Disease Registry. Eligible patients were treated for ≥ years biweekly without clinical events. Every 3 months, switchers to Q3–4W were matched to QW patients by age at diagnosis, referral center follow-up, disease history (bone events, anemia, thrombocytopenia, splenectomy, hepatosplenomegaly) and dose of ERT. The primary outcome was a composite of GD-related events (bone events, anemia, thrombocytopenia). A 0% non-inferiority margin was prespecified. Secondary outcomes were biomarker changes and economic analyses.

Results: Among 80 eligible GD patients, 63 switched to Q3–4W and were matched to a total of 5 QW patients, followed for an average of 6.3 years. No significant difference in the risk of clinical events was observed between groups (hazard ratio: 0.98 [95% CI: 0.54 to .5]). During follow-up, absolute risk difference remained below the 0% non-inferiority threshold at all timepoints. Biomarkers remained stable or slightly decreased in the Q3–4W group. The dosing interval extension led to an average reduction of 55 infusions per patient, corresponding to approximately €450,000 saved per patient over 6 years.

Conclusion: In stable GD patients, extending ERT administration to every 3–4 weeks was non-inferior to the standard biweekly regimen, supporting personalized spacing strategies that may improve quality of life and reduce healthcare costs.

Conflict of Interest: B.H., received travel fees from Sanofi; A.B., received travel fees from Sanofi and Takeda, and consulting fees or other remuneration including fee as speaker from Sanofi and Takeda; F.D., received consulting fees or other remuneration including fee as speaker from Sanofi; B.C., received travel fees from Sanofi and Takeda; F.G., received travel fees from Sanofi; A.M., received fee as speaker from Sanofi and Takeda; M.P., received travel fees from Sanofi, and consulting fees or other remuneration including fee as speaker from Sanofi and Takeda; W.M., received fees for consultancy speaking, travel grants, meetings from Sanofi, Takeda, Amicus therapeutics; Y.N., received research grants by Takeda, and received consulting fee or other remuneration including fee as speaker from Sanofi; assisting in the design of and/or participating in clinical studies using products manufactured by the Sanofi; C.S., received consulting fee or other remuneration including fee as speaker from Takeda and Sanofi; F.C., received fees for consultancy speaking, travel grants, meetings from Sanofi and Takeda; N.B., received fees for consultancy speaking, travel grants, meetings from Sanofi and Takeda.

O36- Safety and efficacy of venglustat versus imiglucerase in patients with Gaucher Disease Type 3 (LEAP2MONO): a phase 3, randomized, double-blind multicenter trial

Eugen Mengel[1], Fatma Derya Bulut[2], Qi Zhang[3], Dmitry Cherkasov[4], Gabriela Perichon[5], Riliang Zheng[5], Kristina An Haack[4], Pramod K Mistry[6]

[1]Institute of Clinical Science for Lysosomal Storage Disorders, SphinCS GmbH, Hochheim, Germany; [2]Cukurova University, Pediatric Metabolism and Nutrition Department, Adana, Turkey; [3]Sanofi, Morristown, NJ, United States; [4]Sanofi, Chilly-Mazarin, Île-de-France, France; [5]Sanofi, Cambridge, MA, United States; [6]Department of Pediatric GI/Hepatology, Yale University School of Medicine, New Haven, CT, USA

Presentation type: Oral Presentation
Poster number: P48 - **Giusto** Room

Gaucher disease type 3 (GD3) is a rare, chronic neuronopathic lysosomal disorder characterized by multisystem involvement and progressive neurological decline. Current enzyme replacement therapies (ERTs) reverse the hematologic, visceral, and bone manifestations but do not achieve meaningful central nervous system (CNS) distribution nor alleviate neurological symptoms. Venglustat, an oral, brain-penetrant glucosylceramide synthase inhibitor, has shown potential to treat CNS manifestations of GD3. LEAP2MONO (NCT05222906) is a Phase 3, randomized, double-blind, double-dummy, active-comparator, multinational, multicenter trial comparing oral venglustat to intravenous imiglucerase in pediatric patients (≥12 to <18 years) and adults with GD3 who were stable on long-term ERT and met predefined therapeutic goals. Eligibility criteria included Scale for Assessment and Rating of Ataxia (SARA) score ≥1 and presence of gaze palsy with slow or absent horizontal saccades. Participants (n=43) were randomized 1:1 to receive 52 weeks of either venglustat (15 mg adults; 12 or 15 mg adolescents) with placebo infusions, or imiglucerase at pre-trial dose with placebo tablets. Primary endpoints are changes from baseline to Week 52 in the SARA modified total score and the Repeatable Battery for the Assessment of Neuropsychological Status total index score. Efficacy secondary endpoints included percentage changes in spleen/liver volume, platelet count, plasma/CSF levels of glucosylceramide and glucosylsphingosine, and change in hemoglobin. Safety secondary endpoints included treatment-emergent adverse events (AE), serious AEs, AEs of special interest, physical and ophthalmological examination, and changes

in the Beck Depression Inventory II (BDI-II) score for participants ≥13 years of age at baseline or Patient Health Questionnaire 9 (PHQ-9) for participants aged 12 years at baseline. Presently, data collection and analyses are ongoing; study updates will be presented at the congress. LEAP2MONO is the first trial evaluating brain-penetrant venglustat in pediatric and adult people living with GD3, targeting both systemic and neurologic manifestations of GD3.

Conflict of Interest: E.M., has received research support, honoraria, and consulting fees from Sanofi; F.D.B., has no conflict of interest; Q.Z.,, D.C., G.P., and K.A.H., are employees of Sanofi and may hold stock/stock options; R.Z., is a former employee of Sanofi and may hold stock/stock options; P.M., is a member of the International Collaborative Gaucher Group (ICGG) Gaucher Registry North American Advisory Board, and has received research support, and travel reimbursement from Sanofi.

O37- Chaperone and antioxidant dual action iminosugar hybrids for Gaucher Disease

Francesca Clemente[1], Alessio Morano[1], Camilla Matassini[1], Damiano Tanini[1], Silvia Falliano[1], Rebecca Sodano[1], Paolo Paoli[1], Andrea Goti[1], Francesca Cardona[1], Amelia Morrone[1]

[1]Department of Chemistry, University of Florence, Via della Lastruccia 3-13, 50019 Sesto Fiorentino

Presentation type: Oral Presentation
Poster number: P49 - **Giusto** Room

Pathogenic variants in GBA1 that compromise the folding and trafficking of glucocerebrosidase (GCase) represent the major pathogenic cause of Gaucher disease (GD) and are increasingly recognized as risk factors for Parkinson's disease. Misfolded GCase is retained in the endoplasmic reticulum, limiting its delivery to lysosomes and leading to reduced enzymatic activity and subsequent cellular dysfunction. Among emerging therapeutic strategies, iminosugar-based pharmacological chaperones have shown particular promise by stabilizing mutant GCase, thereby promoting proper folding and improving lysosomal targeting.

In this work, we present the design, synthesis, and biological evaluation of a novel family of N-alkyl trihydroxypiperidine iminosugar–antioxidant hybrids, in which iminosugar pharmacological chaperones are covalently linked to antioxidant units. Since both GD and PD are characterized by elevated oxidative stress, integrating antioxidant functionalities into the chaperone scaffold was designed to deliver additional therapeutic benefit, simultaneously supporting GCase function and counteracting oxidative damage. This dual-function design is consistent with the multi-target-directed ligand approach, which aims to address complex interconnected pathological mechanisms through a single molecular scaffold. Their effects were quantified by measuring GCase enzymatic activity and intracellular reactive oxygen species (ROS) levels, to assess lysosomal function and redox status in fibroblasts derived from GD patients. The results indicate that these iminosugar–antioxidant hybrids, combining iminosugar chaperone activity with antioxidant properties, can enhance GCase activity while reducing oxidative stress. Overall, these findings support further optimization of iminosugar–antioxidant hybrids as an innovative therapeutic avenue for GD and potentially for related lysosomal storage and neurodegenerative disorders.

Acknowledgments: NGEU funded by MUR for projects MNESYS (PE0000006); MULTIFUN (Prin2022, Project code 2022N9E847); PH- PRISM (Prin2022, Project code 2022FSC2FA); Telethon ETS Foundation and Italian Gaucher Association (GSA22P001); PRIN Bando 2022 Prot.20228S5LWY.

Conflict of Interest: None declared.

O38- Development of a novel systemic AAV gene therapy for neuronopathic Gaucher disease

Tae-Un Han[1], PamelaSara Head[2], Akhil Kulkarni[1] Tiffany Chen[1], Adenrele Gleason[1], Bahafta Berhe[1], Charles P. Venditti[2], **Ellen Sidransky**[1]

[1]Medical Genetics Branch, NHGRI, NIH, United States; [2]Metabolic Medicine Branch, NHGRI, NIH, United States

Presentation type: Oral Presentation
Poster number: P51 - **Giusto** Room

Current enzyme replacement therapy and substrate reduction therapy are effective for non-neuronopathic Gaucher disease (GD), but do not reverse neuronopathic symptoms, as these therapies do not cross the blood-brain-barrier. In this study, we developed novel viral-based gene therapies and evaluated their efficacy in murine models of neuronopathic GD (nGD). To minimize potential genotoxicity caused by high transgene expression levels, codon-adjusted and optimized human *GBA1* constructs were cloned into a gene cassette containing the EF1S promoter and Hepatitis B Virus Posttranscriptional Regulatory Element and then packaged in AAV9 and AAVrh10 capsids. The AAV-hGBA vectors were systemically delivered at varying titration levels via retro orbital injections in the neonatal K14-lnl skin-recovery knock-out mouse, a model of early onset nGD. Both AAV9 and AAVrh10-hGBA1 vectors restored glucocerebrosidase (GCase) levels in H4 cells and in patient iPSC-derived dopaminergic neurons with *GBA1* knockout. K14-lnl mice treated with 4×10^{11} GC/dose of AAV9 and AAVrh10-hGBA1 did not develop manifestations of nGD and their lifespan was extended significantly (> 1 year), with grossly normal behavior, development, weight gain, clinical appearance, and fertility. Overall, the AAV9-hGBA1 showed better efficacy than AAV10-hGBA1. K14-lnl mice treated with AAV9-hGBA1 lack signs of neuroinflammation, and enzyme activity and lipid accumulation were restored back to normal levels. A mouse model of later onset nGD, generated by induced *Gba1* knockout using tamoxifen treatment (TAM-KO), was also used to test the efficacy of the AAV9-hGBA1 construct. AAV9-GBA1 injection of the TAM-KO mice extended their lifespan by 8~28 weeks and corrected both the pathological phenotype and GCase activity and levels. We also tested *in-vitro* infection of AAV9-*coGBA1.1* into a human model using DA neurons derived from human induced pluripotent stem cells (iPSC) carrying a *GBA1* knockout, ademonstrating successful expression of GCase after transduction. In summary, we showed that the EF1s *coGBA1.1* HPRE transgene, when packaged using either an AAV9 or AAVrh10 capsid, demonstrates potent *in vivo* efficacy in mouse models of nGD.

Conflict of Interest: None declared.

Poster Presentations Only (By Category)

Patients' Perspective (Tergeste Room)

P1- Global Commitment, Local Impact: The IGA's Dedication to Gaucher Care in Africa

Vesna Aleksovska[1], Tanya Collin-Histed[2], Christian Hendriksz[3], Derralynn Hughes[4], Engela Helena Conradi[5], Roselyn Kanja-Odero[6], Albe Swanepoel[5], Augustin Ndatinya[7], Aimee Donald[8], Phoebe Wamalwa[9], Kandi-Catherine Muze[10]

[1]International Gaucher Alliance, Bitola, Republic of North Macedonia; [2]International Gaucher Alliance, London, United Kingdom; [3]A Rare Cause, Registered charity in England and Wales, Ilkley, United Kingdom; [4]Royal free London NHS foundation trust and University College, London, United Kingdom; [5]Centre for Human Metabolomics, Desmond Tutu School of Medicine, Faculty of Health Sciences, North-West University, Potchefstroom, South Africa; [6]International Gaucher Alliance, Nairobi, Kenya; [7]Kigali Medical Center Polyclinic, Kigali, Rwanda; [8]Manchester Foundation Trust, Manchester, United Kingdom; [9]Kenyatta University, Nairobi, [10]Kenya; Muhimbili National Hospital, Dar es Salaam, Tanzania

Poster number: P1

The International Gaucher Alliance (IGA) is committed to improving the lives of Gaucher patients globally, with a significantly expanded focus across Africa. This initiative prioritises awareness, timely diagnosis, equitable access to treatment, and sustained patient support, underpinned by strategic collaborations with the International Working Group on Gaucher Disease (IWGGD) and “A Rare Cause.”

The IGA has built a growing network across Africa, with member organisations, Gaucher Leaders, and volunteers supporting patients in South Africa, Kenya, Rwanda, Botswana, Morocco, Tunisia, Tanzania, Ghana, Ethiopia, Sudan, Uganda, Libya, Algeria, Zimbabwe, Namibia, and Egypt.

Education is central to our approach. On 3 October 2025, the IGA hosted the “Empowering Africa: Advancing Gaucher Disease Diagnosis and Care” webinar, convening global experts and regional clinicians. The East Africa Family Meeting in Nairobi on 14 December 2024 featured a CME-accredited webinar and patient networking sessions, engaging participants from Kenya, Tanzania, and Rwanda. It marked a milestone in regional advocacy and community mobilisation, and another meeting is planned for November 2025.

A targeted webinar on the 5th of May 2025 addressed Gaucher Disease in Libya, focusing on diagnosis, management, and the Africa Roadmap. A dedicated educational series on Gaucher Disease Type 3 launched in September 2025 and will continue through 2026, with recordings available via the IGA YouTube channel. Beyond education, the IGA leads the “Africa Roadmap Project” with “A Rare Cause,” aimed at streamlining diagnostic pathways and improving treatment access.

Our humanitarian aid programme, in collaboration with pharmaceutical partners, supports access to therapy in Kenya, Rwanda, Zambia, Botswana, Ethiopia, Sudan, and Uganda, alongside free diagnostic support from specialist laboratories.

These coordinated efforts reflect the IGA’s commitment to addressing systemic healthcare gaps and ensuring that more Gaucher patients across Africa receive timely, effective, and compassionate care.

Conflict of Interest: C.H., Decentra Health -CMO and co-founder; V.A., Annual work programme grants for IGA in 2023, 2024 and 2025 from: Amicus, ISU Axbis, AceLink Therapeutics, Pfizer, Sanofi, Takeda, Spur, Lilley, M6P; D.H., honoraria for consulting advisory boards and speaking at educational meetings from Sanofi, Takeda and Spur Therapeutics; T.C-H., Annual work programme grants in 2023, 2024 and 2025 from: Amicus, ISU Axbis, AceLink Therapeutics, Pfizer, Sanofi, Takeda, Spur, Lilley, M6P. Consulting fees from Takeda and Sanofi. Consulting fees and support to attend meetings from Takeda and Sanofi.

A.D., travel honoraria from Sanofi and honoraria for speaking/consultancy from Sanofi and Prevail (Lilly). All other authors have no conflict to declare.

P4- Case studies on the illness experience with Gaucher Disease type 1 in Brazil: a qualitative and socioanthropological study

Carolina Toneloto[1]

[1]International Gaucher Alliance (IGA), Brazil

Poster number: P4

Type 1 Gaucher Disease is a rare, chronic, and often "invisible" illness that creates distinct personal illness experiences. These were explored in the PhD research “Narratives about the experience with Type 1 Gaucher Disease”, conducted at the University of Campinas (Brazil) by the author.

Using the snowball method, nine individuals were interviewed, and their stories analyzed through qualitative content analysis. Three were selected as case studies.

While “João”* (lawyer, 52 years old) accepted the disease as part of his identity, with a defined place in his life, “José”* (general assistant, 27 years old) claimed to have a health problem, and, although he knew it was Gaucher Disease, he was distressed by not understanding it adequately, looking for more intelligible ways (for himself and others) of explaining it. “Maria” * (graphic designer, 45 years old), on the other hand, doubted her diagnosis, and did not consider herself, in essence, an illness person.

All three associated the disease with enzyme replacement therapy (ERT), which significantly shaped their illness narratives. Despite ERT requiring intravenous administration by medical professionals in hospital settings (in Brazil), patients described it in simplified terms—comparing it to a “detergent” that dissolves the body’s accumulated “fat.” The use of this metaphor seemed to minimize both its importance and its potential risks.

The results show that there is still much to do in educating Brazilian patients about their health, helping them properly understand the complex information about the disease and the available treatments. Furthermore, demonstrate that patients have a specific type of knowledge, which, as it is linked to practical demands, can expand the interests of the scientific community about that, and improve the quality of health services. In addition, demonstrate that patient ´s voices must continue to be heard and understood more clearly in future studies.

*Fictional names.

Conflict of Interest: None declared.

P5- Gaucher Disease: A Case Study in Geographic Disparities of Newborn Screening in the US

Aviva Rosenberg[1], Sora Lichtman[1]

[1]Gaucher Community Alliance, United States

Poster number: P5

Newborn screening is a powerful public health tool for early detection of many disorders. In the United States, wide variations of tested conditions exist across states. Inconsistent standards have led to geographic disparities in diagnosis that can have a profound impact on patient outcomes. Gaucher Disease is a lysosomal storage disorder (LSD), caused by defects in lysosomal function, leading to the accumulation of harmful substances in the body. LSDs are often under-recognized, with delays in diagnosis and treatment. FDA-approved treatments for Gaucher improve survival rates, quality of life, and reduce ongoing costs for treating critical symptoms. Delays in diagnosis lead to irreversible disease effects. An accurate diagnosis of some types of Gaucher disease can be delayed by 7 years or longer and even a small delay in diagnosis for neuronopathic GD can be deadly.

Gaucher disease affects all ethnic groups but has a higher prevalence among the Ashkenazi Jewish population. In the five states with the highest concentration of American Jews, only New Jersey includes Gaucher in its state-wide newborn screening (NBS) panel. New York screens for it in select hospitals, while it is not included in panels in Pennsylvania, Florida and California. The inclusion of Gaucher disease in newborn screening panels in all states represents an opportunity to advance equitable access to early diagnosis and care for affected newborns. This presentation will describe the case for including Gaucher in NBS panels, the challenges of changing newborn screening panels in a country with 50 diverse states, and the impact of failing to screen.

Participants will (be able to)

1. Critique regional differences in newborn screening panels

2. Understand the benefits of early detection for lysosomal storage disorders

3. Express the challenges in adding LSD to newborn screening panels

Conflict of Interest: Gaucher Community Alliance receives support from Takeda, Sanofi, Pfizer and Eli Lilly for its newborn screening advocacy work.

P6- Beyond the Clinic: Empowering Self-Management and Living Well with Gaucher Disease

Carolina Toneloto[1], Irena Znidar[2], Magy Abdelwahab[3], Sara Khan[4], Sintia Tamele[5], Shoshana Revel-Vilk[6], Tanya Collin-Histed[4], Vesna Aleksovska[7]

[1]International Gaucher Alliance, Sao Paulo, Brazil;[2]International Gaucher Alliance, Ljubljana, Slovenia; [3]Cairo University Pediatric Hospital, Cairo, Egypt; [4]International Gaucher Alliance, London, United Kingdom; [5]International Gaucher Alliance, Maputo, Mozambique; [6]Pediatric Haematology/Oncology Unit, Shaare Zedek Medical Centre, Jerusalem, Israel; [7]International Gaucher Alliance, Bitola, Republic of North Macedonia

Poster number: P6

This abstract presents a strategic framework of recommendations aimed at improving clinical outcomes and enhancing the quality of life for individuals living with Gaucher Disease (GD). Recognising that GD management extends beyond episodic clinical encounters, the proposed model integrates structured patient self-management into routine care, underpinned by three interdependent principles: empowerment, collaboration, and holistic support.

Empowerment: The recommendations position patients and caregivers as continuous experts in their lived experience of GD. By acknowledging and integrating this experiential knowledge, healthcare professionals (HCPs) can foster patient self-efficacy, enabling individuals to actively manage symptoms, anticipate challenges, and engage meaningfully in care decisions. This shift from being a passive care recipient to an informed partner is essential for navigating long-term disease management.

Collaboration: The framework advocates for bidirectional data exchange, where patient-reported outcomes—such as symptom diaries and quality-of-life metrics—are valued alongside clinical assessments. This approach supports personalised treatment planning, optimises adherence, and enhances therapeutic alliance. Shared decision-making is central, promoting transparency, trust, and more targeted interventions.

Holistic Support: Beyond clinical parameters, the recommendations address psychosocial determinants of health, particularly during vulnerable life stages such as diagnosis, adolescence, and transition to adult care. A multidisciplinary model is encouraged, involving family, allied health professionals, and social support systems. Integration of co-morbidity management within GD care pathways is also prioritised.

Collectively, these recommendations offer actionable guidance for embedding patient-centred, collaborative care into GD management. By aligning clinical expertise with patient insight and psychosocial context, the model aims to reduce complications, improve health outcomes, and elevate the lived experience of those affected by GD.

Conflict of Interest: V.A., Annual work programme grants for IGA in 2023, 2024 and 2025 from: Amicus, ISU Axbis, AceLink Therapeutics, Pfizer, Sanofi, Takeda, Spur, Lilley, M6P; T.C-.H, Annual work programme grants in 2023, 2024 and 2025 from: Amicus, ISU Axbis, AceLink Therapeutics, Pfizer, Sanofi, Takeda, Spur, Lilley, M6P. Consulting fees from Takeda and Sanofi. Consulting fees and support to attend meetings from Takeda and Sanofi; C.T., Support fees to attend meetings from Sanofi (Brazil); S.R.-V., The SZMC Gaucher Unit receives support from Sanofi/ for participation in the ICGG Registry and from Takeda for the GOS Registry. S.R.-V. receives honoraria, support for attending meetings, and/or travel, and advisory fees from Takeda and Sanofi; I.Z., Annual work programme grants in 2023, 2024 and 2025 from: Amicus, ISU Axbis, AceLink Therapeutics, Pfizer, Sanofi, Takeda, Spur, Lilley, M6P; All other authors have no disclosures to declare

P7- Patient considerations for potential AAV gene therapy for Gaucher Disease type 1

Aviva Rosenberg[1,2], Tanya Collin-Histed[1], Cynthia Frank[2], Raul Chertkoff[1,3], Pamela Foulds[4], Philip Yin[4], Dan Wolf[4], Simon Flynn[4]

[1]InternaΘonal Gaucher Alliance, London, United Kingdom; [2]Gaucher Community Alliance, Pittsburgh, USA; [3]Israeli Gaucher Association, Haifa, Israel; [4]Spur Therapeutics, Stevenage, United Kingdom

Poster number: P7

Gaucher disease type 1 is a lysosomal storage disorder. Treatment options include enzyme replacement therapy (ERT), typically infused every 2 weeks for life, or substrate reduction therapy (SRT), an oral option that requires daily dosing and can be limited by tolerability and other contraindications.

AAV gene therapy (GT) is a potential one-time treatment replacing the need for chronic ERT/SRT with similar or possibly better outcomes. GT enables the body to produce GCase, the enzyme

deficient in people with Gaucher disease. GCase is continuously released into the blood stream, where it is always available for cell uptake.

Currently, GT is only accessible through clinical trials, although the possibility of this potential new therapeutic option creates interesting considerations for patients. Assuming success and approval, patients and their families will need to consider various aspects in their decision making. Not all patients will be eligible for GT due to past exposure to the viral capsid used to deliver the healthy gene, with resultant antibodies preventing its uptake. A simple blood test will assess eligibility.

If eligible to receive GT, patients will need to consider such factors as 1) desire to potentially be free of chronic ERT/SRT versus the stability of the current treatment routine; 2) lifestyle interests such as travel or moving, unrestricted by ERT dosing needs or loss of insurance anxiety; 3) the potential for improved clinical outcomes versus the unknown extent of GT durability- as long-term data is unlikely to be available at the time of any approval; 4) long-term risks of GT versus the potential to reduce the risk of long-term Gaucher complications; 5) reduced ERT/SRT access in some countries; 6) risks of a course of immunosuppression to prevent/lessen an immune response to the initial GT delivery and many other factors in consultation with their medical provider.

Conflict of Interest: P.F., D.W., and S.F. are employees of Spur Therapeutics. P.Y. is a former employee of Spur Therapeutics.

P8- How is to live with type 1 Gaucher disease in Brazil and the Netherlands: case studies through illness narratives

Carolina Toneloto[1], Jan Timmerman[2]

[1]International Gaucher Alliance, Sao Paulo, Brazil; [2]International Gaucher Alliance, the Netherlands

Poster number: P8

Gaucher disease is an inborn error of metabolism and the most prevalent lysosomal storage disorder. It is a chronic, progressive, autosomal recessive condition caused by deficiency of the enzyme β-glucosidase (glucocerebrosidase) and is classified into three types based on neurological involvement, with Type 1 being the least severe.

Illness narratives are a valuable approach to understanding how individuals experience chronic conditions, as they reveal how people interpret and manage daily life while living with illness and how this process can influence quality of life. In the context of Type 1 Gaucher disease—a rare condition whose standard treatment, enzyme replacement therapy (ERT), presents challenges to long-term adherence—such narratives offer important insights into the personal and biographical impact of both the disease and its treatment.

This study examines the authors' own illness narratives, focusing on key moments in their trajectories, including life before diagnosis, the diagnostic journey, adherence to ERT, and life after diagnosis. Particular attention is given to the practical and emotional dimensions of living with Gaucher disease, as well as experiences related to healthy exercise and nutrition and their perceived impact on quality of life.

The study also explores living with Type 1 Gaucher disease in two distinct sociocultural contexts—Brazil and the Netherlands—highlighting how differences in culture, social support, and healthcare systems shape illness experiences. While many aspects of living with the

disease are shared, distinct features emerge from the authors' differing environments and healthcare structures.

Overall, the findings demonstrate that illness narratives are a valuable strategy for deepening understanding of Gaucher disease, fostering scientific and clinical interest, and contributing to improvements in healthcare delivery and quality of life for individuals living with this rare condition.

Conflict of Interest: None declared.

P9- The GD3 Community Advisory Board: Amplifying the Patient and Caregiver Voice in Neuronopathic Gaucher Disease

Tanya Collin-Histed[1], Madeline Stoodley[2], Irma Shah[3], Theresa Sweeney[4], Merissa Zuzulock[5], Amanda Regalado[6], Hussein Fadhil[7], Beenish Ayub[8], Maurice Moure[9], Andre Balzekiene[10], Vit Hubeny[11]

[1]International Gaucher Alliance, London, United Kingdom; [2]International Gaucher Alliance, Bath, United Kingdom; [3]International Gaucher Alliance, Reading, United Kingdom; [4]International Gaucher Alliance, Lakewood, United States; [5]International Gaucher Alliance, New Jersey, United States; [6]International Gaucher Alliance, Midlothian, United States; [7]International Gaucher Alliance, Gothenburg, Sweden; [8]International Gaucher Alliance, Sindh, Pakistan; [9]International Gaucher Alliance, Bayern, Germany; [10]International Gaucher Alliance, Vilnius, Lithuania; [11]International Gaucher Alliance, Zlonin, Czech Republic

Poster number: P9

Background: Neuronopathic Gaucher disease (GD3) remains one of the most complex and underserved forms of Gaucher disease, with significant unmet needs in diagnosis, education, research, and access to care. To address these challenges, the International Gaucher Alliance (IGA) established the GD3 Community Advisory Board (CAB) in 2025. The CAB provides a global, patient- and caregiver-led platform to ensure that lived experience directly informs and shapes research priorities, advocacy strategies, and awareness initiatives.

Aim: To create a structured and sustainable mechanism through which people living with GD3 and their caregivers can identify community priorities, engage in meaningful consultation with external stakeholders, and guide the development of inclusive, patient-centred solutions.

Methods / Activities: The CAB is composed entirely of individuals living with GD3 and caregivers representing diverse geographical regions. The group held its inaugural meeting in June 2025 and meets quarterly. Each meeting focuses on a specific theme of importance to the community.

- Meeting 1: Identified key unmet needs for people with GD3 and their families. These are now being further explored through a global online consultation to capture wider perspectives.
- Meeting 2: Focused on educational challenges, leading to the development of an awareness and resource programme to support learning and inclusion for children and young people with GD3.

The CAB will also serve as a focus group for external consultation on GD3-related topics by researchers, clinicians, and policymakers. It will contribute to the design of a new neuronopathic Gaucher disease (nGD) repository encompassing GD2 and GD3.

Anticipated Outcomes / Impact: Expected outcomes include a published summary of community-identified needs, creation of educational tools, strengthened stakeholder collaboration, and a scalable model to extend to GD2 in 2026. The GD3 CAB exemplifies how patient-led structures can drive equitable progress in rare disease care and research.

Conflict of Interest: T.C.-H., A.B., M.S., are either Staff or Board of the IGA that receives annual grants from various pharmaceutical companies to support their annual work programme.

P10- International Gaucher Day 2025 Marks a Global Month of Awareness

Andre Balzekiene[1], Vesna Aleksovska[2], Aimee Kate-Bosch[3], Suyog Sathe[4], Tanya Collin-Histed[5], Maddie Stoodley[5]

[1]International Gaucher Alliance, Vilnius, Lithuania; [2]International Gaucher Alliance, Bitola, Republic of North Macedonia; [3]International Gaucher Alliance, Cape Town, South Africa; [4]International Gaucher Alliance, Mumbai, India; [5]International Gaucher Alliance, London, United Kingdom

Poster number: P10

Background: Launched in 2014, International Gaucher Day (IGD) aims to raise awareness of Gaucher disease—a rare inherited metabolic disorder—and improve outcomes for patients worldwide. Coordinated by the International Gaucher Alliance (IGA), IGD unites patients, clinicians, researchers, and advocates to drive change and foster collaboration.

Aim: In 2025, the IGA expanded IGD into a month-long campaign throughout October under the theme "See the Signs, Shorten the Diagnostic Journey." The initiative aimed to increase recognition of early signs of Gaucher disease, reduce diagnostic delays, and improve access to care, while inspiring collective advocacy and renewed hope.

Methods / Activities: The centrepiece was an interactive IGD Awareness Calendar, revealed daily on IGA's social media channels to share stories, testimonials, and videos from 25 countries—creating a global portrait of the Gaucher community. The campaign followed five phases:

- Defining the theme and developing 31 diverse posts (videos, quotes, surveys, infographics).
- Creating a unified visual identity with a graphic designer using a dedicated design tool.
- Collecting and adapting patient and clinician stories for digital formats.
- Launching and promoting the campaign, including a multilingual infographic package (English, Spanish, German, French, Portuguese, Arabic) shared with IGA members. Daily content on Facebook and Instagram was boosted by professional media planning to extend reach beyond the Gaucher community.
- Evaluating outcomes against the 2024 campaign.

Outcomes / Impact: IGD Awareness Month 2025 achieved major growth in visibility, reaching over 2 million unique users—up from thousands in 2024. Engagement across organic and paid content nearly doubled, and IGA's following expanded significantly. Most importantly, the campaign amplified global voices and strengthened unity within the Gaucher disease community as never before.

Conflict of Interest: IGA., IGA received annual work programme grants in 2023, 2024 and 2025 from: Amicus, ISU Axbis, AceLink Therapeutics, Pfizer, Sanofi, Takeda, Spur, Lilley, M6P; V.Al., Annual work programme grants for IGA in 2023, 2024 and 2025 from: Amicus, ISU Axbis, AceLink Therapeutics, Pfizer,

Sanofi, Takeda, Spur, Lilley, M6P; T.C.-H., Annual work programme grants in 2023, 2024 and 2025 from: Amicus, ISU Axbis, AceLink Therapeutics, Pfizer, Sanofi, Takeda, Spur, Lilley, M6P. Consulting fees from Takeda and Sanofi. Consulting fees and support to attend meetings from Takeda and Sanofi; M.S., Annual work programme grants for IGA in 2023, 2024 and 2025 from: Amicus, ISU Axbis, AceLink Therapeutics, Pfizer, Sanofi, Takeda, Spur, Lilley, M6P.

Laboratory – Genetics, Biochemistry & New Developments (Giusto Room)

P16- Not all elevated Lyso-Gb1 is Gaucher disease: case report of myoclonic epilepsy associated with a SCARB2 mutation

Vinicius Lima Ferraz[1], Emilly de Jesus Garcia Ataide[1], Fabiano Oliveira Poswar[1], Ida Vanessa Doederlein Schwartz[1]

[1]Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil

Poster number: P16

Lyso-Gb1 is an established biomarker for Gaucher disease, but its interpretation is not always straightforward. Increased levels may also be seen in disorders that interfere with intracellular glucocerebrosidase trafficking, including LIMP-2 deficiency caused by pathogenic variants in SCARB2. We report a 27-year-old woman, born to consanguineous parents, who developed action- and stress-induced myoclonus at 22 years of age. Over time, her neurological symptoms progressed and were accompanied by renal involvement, characterized by persistent nephrotic-range proteinuria, hypoalbuminemia, anemia, and gradual decline in renal function. Family history was notable for a sister and a cousin with a similar neuro–renal phenotype who died at a young age. At her most recent evaluation, the patient was fully oriented and functionally independent, with mild dysmetria on examination and no spontaneous myoclonus at rest. Biochemical assessment showed elevated chitotriosidase (254 nmol/h/mL; RR: 8.8–132) and Lyso-Gb1 (30.49 nmol/L; RR: 3–12), along with reduced β-glucocerebrosidase activity (5.7 nmol/h/mg prot; RR: 10–45), initially raising suspicion of Gaucher disease. Genetic testing subsequently identified a homozygous pathogenic variant in SCARB2 (c.88C>T; p.Gln30*), confirming the diagnosis of Action Myoclonus–Renal Failure syndrome. Miglustat therapy was started, and dose escalation to 600 mg/day was followed by worsening tremor, which improved after dose reduction to 300 mg/day. This case illustrates that Lyso-Gb1 elevation may reflect secondary lysosomal dysfunction rather than primary Gaucher disease, since impaired delivery of glucocerebrosidase to lysosomes can lead to glycosphingolipid accumulation despite preserved enzyme synthesis. Reliance on biomarkers alone may therefore be misleading; careful integration of clinical findings, biochemical data, and molecular analysis remains essential for accurate diagnosis and optimal management of lysosomal storage disorders.

Conflict of Interest: None declared.

P17- Correlation of circulating Growth Differentiation Factor-15 (GDF-15) levels with laboratory and clinical indices in patients with Gaucher Disease type I

Veroniki Komninaka[1], Aimilia Mantzou[2], Nikolaos Tsagarakis[1], Kostantinos Karkaletsis[3], Ioulia Chaliori[1], Dimitrios Liakopoulos[1], Stefanos Papadhimitriou[1], Sofia Chaniotaki[1], Theodoros Marinakis[4], Christos Poziopoulos[5], Helen Pergantou[6], Ioannis Papassotiriou[2]

[1]Hematology Laboratory, General Hospital of Athens "G. Gennimatas", Athens, Greece; [2]First Department of Pediatrics, National and Kapodistrian University of Athens, School of Medicine, Athens, Greece; [3]Athens Medical Center, Paleo Faliro Clinic, Athens, Greece; [4]Hematology Clinic, General Hospital of Athens "G. Gennimatas", Athens, Greece [5]Department of Hematology, METROPOLITAN Hospital, Athens, Greece; [6]Haemophilia Centre/Haemostasis and Thrombosis Unit, "Aghia Sophia" Children's Hospital, Athens, Greece

Poster number: P17

Introduction: Growth Differentiation Factor 15 (GDF-15), a divergent member of the TGFβ superfamily, controls hematopoietic growth, energy homeostasis, adipose tissue metabolism, body growth, bone remodelling, and response to stress signals. Its' significant role has been reported in cancers, cardiometabolic disorders, mitochondrial and other diseases, while in non-mitochondrial diseases such as Gaucher disease (GD) the reports are limited.

Aim: To evaluate possible correlations of circulating GDF-15 with GD activity, spleen and liver volume, bone deformities as well as genotype.

Patients and Methods: Thirty adult patients under enzyme replacement therapy were included in the study, while 20 healthy individuals were served as controls. Along with measurements of specific hematologic and blood chemistry parameters related to GD, GDF-15 levels were measured using the Roche Cobas e411 immunoassay automated analyzer (Roche Diagnostics, Rotkreuz, CH). Results were expressed as Mean±SEM, while to linearize correlation models log transformations were used when appropriate.

Results: GDF-15 levels, a) were significantly higher in patients, 3,147±1,316ng/mL (range, 390.0-18,381.0ng/mL) compared to controls, 665.0±50.9ng/mL (range, 269.6-1,129.0ng/mL), $p<0.001$, and they were independent of patients' age ($p>0.106$); b) were significantly correlated with Hb =-0.534, p=0.02, PLT r=-0.602, p=0.008, RDW r=0.805, $p<0.001$, Fe r=-0.744, $p<0.001$ and ferritin r=0.617, p=0.006; higher GDF-15 levels were associated with lower total and HDL-cholesterol concentrations ($p<0.01$), c) were significantly correlated with chitotriosidase activity r=0.606, $p<0.001$, spleen volume r=0.633, p=0.009, and Bone Mineral Density, measurements for L1-L4 vertebrae r= -0.581, $p<0.01$ and d) decreased slowly with enzyme replacement therapy r=-0.461, p=0.053, slope -0.060 comparing to decline of chitotriosidase activity r=-0.649, p=0.004, slope -2.3 and ferritin levels r=-0.730, $p<0.001$, slope -1.8, respectively.

Conclusions: GDF-15 levels correlated significantly with clinical and laboratory features of GD, indicating a significant multifactorial role of this cytokine in these patients. However, further large-scale longitudinal studies are necessary to evaluate its potential role as a GD biomarker.

Conflict of Interest: None declared.

P18- Beyond classical biomarkers: endocrine and molecular contributors to bone involvement in Gaucher disease

Irene Serrano-Gonzalo[1], Sonia Roca-Esteve S[1], Isidro Arévalo-Vargas[1], Ralf Köhler[1], Pilar Giraldo[1]

[1]Fundación Española para el Estudio y Terapéutica de la Enfermedad de Gaucher

Poster number: P18

Skeletal involvement is a major source of morbidity in Gaucher disease (GD), arising from interactions between disease burden, bone remodeling, and systemic regulators. While

alterations in parathyroid hormone (PTH) and vitamin D have been reported, the mechanisms linking endocrine regulation to bone pathology remain unclear. MicroRNAs (miRNAs) are key post-transcriptional regulators of bone homeostasis, but their relationship with PTH in GD has not been explored.

We evaluated a cohort of GD patients for skeletal involvement using Spanish MRI (S-MRI) and DXA. Circulating PTH, vitamin D, and classical GD biomarkers (chitotriosidase activity, CCL18/PARC, glucosylsphingosine) were measured. The expression of three bone-related miRNAs was analyzed, and associations with PTH, skeletal parameters, and classical biomarkers were assessed.

Thirty patients with a median (Q1-Q3) age of 32.0 (23.00-53.00) years were included. Bone mineral density loss occurred in 37%, intraosseous vascular events in 20%, and bone crises in 17%. Median S-MRI score was 7.0 (1.5–10.0). Classical biomarkers did not correlate with PTH or miRNA levels. In contrast, both PTH and miRNA profiles varied according to skeletal involvement. Although no direct association existed between PTH and miRNAs, each independently related to bone status, providing complementary information beyond classical disease markers.

These results suggest that skeletal involvement in GD is driven by multiple, partially independent factors. Classical biomarkers poorly reflect bone pathology, whereas PTH and bone-associated miRNAs may capture distinct aspects of bone remodeling and quality. This highlights the complexity of skeletal disease in GD and supports integrative approaches combining imaging, endocrine markers, and molecular regulators. Ongoing studies, including larger cohorts and additional modulators such as vitamin D, aim to further elucidate these relationships.

Conflict of Interest: P.G., received research grants from Sanofi and Takeda. I.S.-G., All other authors declare no conflicts of interest.

P19- MicroRNAs Reshape Lysosomal–Autophagy Adaptive States in CRISPR-Engineered Neuronal Models of Neuronopathic Gaucher Disease

Isabelle Della Pasqua Bussons[1], Rodrigo Tzovenos Starosta[2], Filippo Pinto e Vairo[3], Thaís Cardoso Bitencourt[4], Lucas Kich Grun[4], Mariane Jaeger[5], Andrew Oliveira Silva[4], Clévia Rosset[4], Kristiane Michelin Tirelli[4], Fernanda Bender Pasetto[4], Fernanda Medeiros Sebastião[4], Tatiéle Nalin[4], Rafael Zimmer[4], Thayne Kowalski[4], Mariana Recamonde-Mendoza[1], Ursula Matte[4], Ida Vanessa Doederlein Schwartz[1], Roberto Giugliani[6], Fernanda Visioli[1], Eduardo Cremonese Filippi Chiela[1], Roselena Schuh[1], Édina Poletto[7], Guilherme Baldo[1], Marina Siebert[8]

[1]Universidade Federal do Rio Grande do Sul (UFRGS), Porto Alegre, Brazil; [2]Oregon Health and Science University (OHSU), Portland, United States; [3]Mayo Clinic, Rochester, United States; [4]Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil; [5]Instituto do Câncer Infantil (ICI), Porto Alegre, Brazil; [6]Centro de Atenção Integral e Treinamento em Doenças Raras, Casa dos Raros, Brasil; [7]Stanford University, Stanford, United States;[8]Graduate Program in Gastroenterology and Hepatology/Universidade Federal do Rio Grande do Sul (UFRGS), Porto Alegre, Brazil

Poster number: P19

Genotype–phenotype correlations are limited in neuronopathic Gaucher disease (GD) forms, where patients carrying severe GBA1 mutations may develop distinct neurological outcomes. This indicates that neuronal adaptive status, rather than enzymatic deficiency, contributes to

disease heterogeneity. MicroRNAs (miRNAs) have emerged as modifiers of lysosomal and autophagy pathways, yet their role in disease-relevant neuronal contexts remains undefined. To investigate whether candidate miRNAs modulate autophagy–lysosomal status in neuronal models of neuronopathic GD, CRISPR/Cas9 knock-in SH-SY5Y neuronal models carrying severe, patient-relevant GBA1 genotypes were generated and validated by Sanger sequencing, glucocerebrosidase (GCase) activity, and β-galactosidase assays. Candidate miRNAs were selected based on expression profiling in blood samples from GD type 1 patients and healthy controls. Wild-type and edited cells were forward transfected with selected miRNAs and appropriate controls. Seventy-two hours post-transfection, cell viability, acidic vesicular compartments, and senescence-associated signaling were assessed by propidium iodide, acridine orange, and C12-FDG staining using flow cytometry. Expression of genes related to autophagy, lysosomal biogenesis, ABC transporters, α-synuclein, and GBA1 was evaluated by qPCR. Despite similarly profound reductions in GBA1 expression and near-abolition of GCase activity, distinct genotype-dependent neuronal status emerged. Cells homozygous for a severe RecNciI genotype exhibited a reactive profile characterized by induction of autophagy-related genes, p62 accumulation, lysosomal biogenesis markers, and α-synuclein upregulation, consistent with maladaptive lysosomal stress. In contrast, cells carrying the N370S+del55pb genotype displayed attenuation of autophagy–lysosomal transcriptional status and minimal α-synuclein induction, indicating a hypo-adaptive state. miRNA transfection in the reactive genotype revealed divergent effects, ranging from cytotoxicity to balanced modulation of lysosomal–autophagy pathways without loss of viability, enabling functional stratification of candidate miRNAs. Neuronopathic GBA1 variants define distinct neuronal adaptive status independent of enzymatic deficiency. Selected miRNAs differentially modulate lysosomal–autophagy pathways in a genotype-dependent manner, supporting their role as modifiers and highlighting miRNA-based strategies for CNS-directed therapeutic development in GD.

Conflict of Interest: None declared.

P20- Optimizing Gaucher Disease Screening: A Comparative Study of Three Mass Spectrometry Methods

Martina Ferro[1], Susanna Del Piccolo[1], Silvia Cattarossi[1], Dania Ferino[1], Tanja Zappamiglio[1], Jessica Biasizzo[1], Andrea Dardis[1]

[1]Department of Medical Area, University of Udine, Udine, Italy

Poster number: P20

Background: Gaucher disease (GD) diagnosis relies on assessment of β-glucosidase (BGLU) activity, glucosylsphingosine (GlcSph) levels, and GBA1 genotyping. HPLC-MS/MS methods allow accurate measurement of BGLU activity and GlcSph in dried blood spots (DBS), facilitating practical screening. This study aimed to validate and compare three methods for assessing GlcSph in DBS and plasma, and BGLU activity in DBS, to establish a reliable workflow for GD screening.

Methods: Enzyme activity in DBS was measured with the commercial NeoLSD MSMS kit (Revvity). Biomarker analysis in DBS and plasma used home-made protocols with isotopically labeled internal standards in extraction solutions. Plasma processing included protein precipitation, while DBS samples were punched and extracted after drying from finger-prick collection. All assays were performed on an HPLC-MS/MS system (Nexera Shimadzu-SCIEX Qtrap 6500 Citrine) using positive ESI and MRM mode.

Results and Conclusions: The precision of the methods was evaluated on ≥15 replicates at three concentration levels, with mean CVs of 15.2% (BGLU), 9.2% (DBS GlcSph), and 7.2% (plasma GlcSph). ROC curve analysis established cut-offs of 9.46 ng/mL (DBS GlcSph), 2.53 ng/mL (plasma GlcSph), and 1.53 µM/h (BGLU), all with 100% sensitivity and specificity. Thirteen Gaucher patients (6M/7F; 46.0 ± 17.5 years) showed uniformly low enzymatic activity (1.12 ± 0.19 µM/h) and were correctly identified by semiquantitative enzymatic screening. Positive results were followed by GlcSph measurement on the same DBS, and then in plasma for confirmation. No correlation between BGLU activity and GlcSph levels has been found. Conversely, GlcSph levels showed good correlation between DBS and plasma (slope = 0.40; R^2 = 0.910).

In conclusion, mass spectrometry–based assays offer reliable tools for GD screening. We recommend simultaneous measurement of BGLU and GlcSph in the same DBS to optimize screening efficiency. Given its higher precision, plasma GlcSph measurement remains the preferred method for monitoring patients over time.

Conflict of Interest: None declared.

P21- Biochemical Characterization of Patients with Gaucher Disease at a Reference Center in Southern Brazil

Kristiane Michelin Tirelli[1], Fernanda Medeiros Sebastião[1], Fernanda Bender Pasetto[1], Inamara Moraes[1], Ida Vanessa Doederlein Schwartz[1]

[1]Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil

Poster number: P21

Background: Gaucher disease (GD) is an autosomal recessive lysosomal storage disorder caused by deficiency of the enzyme glucocerebrosidase (GCase), leading to accumulation of glucocerebroside in monocytes and macrophages, mainly affecting liver, spleen, bone marrow, and other organs. Clinical manifestations include anemia, thrombocytopenia, hepatosplenomegaly, bone pain, and neurological involvement in severe forms. Early diagnosis is essential to initiate therapy and prevent disease progression. Chitotriosidase (CT) is an important biomarker for diagnosis and monitoring. Since 1982, the Medical Genetics Service of the Hospital de Clínicas de Porto Alegre (MGS/HCPA) has acted as a national reference center.

Objectives: To characterize the biochemical profile of patients with Gaucher disease followed at a reference center in southern Brazil.

Methods: This observational, retrospective study was based on a review of medical records. Collected data included sex, age, registration and diagnosis dates, GCase and CT activities, hemoglobin, platelet counts, ferritin levels, and disease subtype.

Results: A total of 44 patients were included (18 males, 43%; 25 females, 57%). GCase activity was reduced in all patients (0.38–2.6 nmol/h/mg protein; reference range: 10–45). Elevated CT activity was observed in 70% (2,076–42,187 nmol/h/mL; reference range: 8.8–132). Thrombocytopenia occurred in 47%, normal platelet counts in 53%, and elevated ferritin levels in 35%. Most patients had GD type 1 (91%), while 9% had GD type 3.

Conclusion: The biochemical profile observed in this cohort highlights the importance of GCase and CT measurements for the diagnosis and follow-up of patients with Gaucher disease. These parameters are essential for monitoring treatment response and disease progression in

patients receiving enzyme replacement or substrate reduction therapy, contributing to improved clinical management and quality of life.

Acknowledgments: MGS/HCPA, CNPq, FAPERGS.

Conflict of Interest: None declared.

P22- Does the HFE gene impact iron metabolism in Gaucher disease patients? An exploratory study

Lucas Ferreira Teixeira[1], Mariana Marcano-Ruiz[1], Gabriela Ponte de Mattos[2], Amanda Pasqualotto[1], Júlia Cordeiro Milke[1], Devora Natalia Randon[1], Suélen Basgalupp[1], Rodrigo T. Starosta[3], Ida Vanessa Doederlein Schwartz[1]

[1]Universidade Federal do Rio Grande do Sul (UFRGS), Porto Alegre, Brazil; [2]Pontifical Catholic University of Rio Grande do Sul, Porto Alegre, Brazil; [3]Oregon Health and Science University, Portland, Oregon, United States

Poster number: P22

Background: Gaucher Disease (GD), a lysosomal disorder caused by biallelic GBA1 variants, often presents with hyperferritinemia, a finding that mimics primary iron overload disorders like Hereditary Hemochromatosis (HH), which is primarily associated with HFE gene variants, most commonly p.Cys282Tyr and p.His63Asp. Given GD's clinical heterogeneity, HFE variants have been proposed as genetic modifiers that might exacerbate iron dysregulation beyond the effects of GD alone. Aim: To investigate alterations in iron metabolism biomarkers in GD and their relation to HFE variants. Methods: We analyzed 37 GD patients, measuring serum ferritin, transferrin saturation (TSAT), serum iron, and total iron-binding capacity (TIBC). For analysis, the highest values of ferritin and TSAT were considered. The complete parallel sequencing of the HFE gene was performed in all patients. Patients were stratified into TSAT >50% (Group A, n=6) and ≤50% (Group B, n=31) to compare the frequency of HFE variants. Fisher's Exact Test was used for statistical analysis. Results: Ferritin levels varied widely across patients (146–3736 ng/mL; median 971 ng/mL, IQR 619–1469), as did TSAT (12.6–86.3%; median 41.2%, IQR 31.2–49.6%), serum iron (35–253 µg/dL; median 118 µg/dL, IQR 92–124), and TIBC (34–359 µg/dL; median 171 µg/dL, IQR 144–218). Three patients were heterozygous for p.Cys282Tyr, four for p.His63Asp, and no p.Ser65Cys carriers were identified. Overall, 18.9% (7/37) of patients carried at least one HFE variant.Carriers of any HFE variant did not differ from non-carriers regarding any biomarker (all $p > 0.05$). Groups A and B did not differ in the frequency of HFE variants. Discussion and Conclusion: These findings suggest that, in this cohort, heterozygous HFE variants do not statistically significantly influence iron biomarker levels. The effect of other genes involved in iron metabolism will be investigated. Higher levels of TSAT may not predict the presence of variants in HFE. So, the best indications for sequencing the HFE gene in the context of hyperferritinemia in GD disease are still to be elucidated.

Conflict of Interest: None declared.

P23- HEPES in cell culture alters the multi-omics profile exhibited by Gaucher disease fibroblasts

Eleonore M. Corazolla[1], Bauke V. Schomakers[1], Maria M. Trętowicz[1], Jill Hermans[1], Michel van Weeghel[1], Frédéric M. Vaz[1], Mia L. Pras-Raves[1], Karen Ghauharali-van der Vlugt[1], Femke S.

Beers-Stet[1], Susanna M.I. Goorden[1], Judith Jansen-Meijer[1], Georges E. Janssens[1], Carla E.M. Hollak[1], Riekelt H. Houtkooper[1], André B. P. van Kuilenburg[1]

[1]Amsterdam UMC location University of Amsterdam

Poster number: P23

Lysosomal function can be affected by components in cell culture. This in turn may influence cellular metabolism and, consequently, research and diagnostics outcomes. One such component is the commonly used pH buffer HEPES. HEPES specifically impacts the trafficking of the lysosomal enzyme glucocerebrosidase, which is deficient in Gaucher disease (GD). Understanding how HEPES affects cellular models of GD is essential, since glucocerebrosidase is central to diagnostic testing and the investigation of GD pathophysiology. Therefore, we examined the broader effects of HEPES on cultured fibroblasts from individuals with GD and healthy controls.

We cultured dermal fibroblasts of eight adults with GD and seven healthy age- and sex-matched controls. The cells were cultured in two culture media, Ham's F10 and DMEM, both with and without HEPES. We assessed glucocerebrosidase enzyme activity and sphingolipid concentrations using a quantitative UPLC-MS/MS method. Additionally, we conducted multi-omics analyses, consisting of lipidomics, metabolomics and proteomics, to explore the broader impact of HEPES in cell culture on fibroblasts.

Glucocerebrosidase activity in cell lysates increased after HEPES exposure in both GD and control fibroblasts, to an extent that may influence diagnostic outcomes. In GD fibroblasts, substrate accumulation was absent and not altered by HEPES exposure. GD fibroblasts exhibited a multi-omics profile largely overlapping with healthy controls and lacking the typical pathological features associated with GD in other cell types, such as mitochondrial dysfunction, dysregulated autophagy, disruption of intracellular calcium homeostasis, ER stress and chronic oxidative stress. In addition, the multi-omics profile was altered by HEPES, however in a non-specific manner.

HEPES influences fibroblasts in culture, both from healthy controls and from patients with GD. Furthermore, GD fibroblasts lack a specific disease-related profile. This renders cultured fibroblasts unsuitable for studying pathological processes in GD. Culturing GD fibroblasts with HEPES may compromise the reliability of diagnostics.

Conflict of Interest: C.H., is involved in pre-marketing studies with Sanofi and Chiesi. All other authors declare no conflicts of interests.

P24- Storage macrophages in spleen of patients with Niemann Pick type B and Gaucher disease

Martijn J.C. van der Lienden[1,2,5], Eline C.B. Eskes[2], Pathma Muthukottiappan[3], Sanne van der Niet[4], Nike Claessen[5], Nicole N. van der Wel[4], Jan Aten[5], Dominic Winter[3], Carla E.M. Hollak[2], Johannes M.F.G. Aerts[1]

[1]Department Medical Biochemistry, Leiden University, 2333 CC Leiden, The Netherlands; [2]Department of Endocrinology and Metabolism, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands; [3]Institute for Biochemistry and Molecular Biology, Medical Faculty, Rheinische Friedrich-Wilhelms-University of Bonn, 53115 Bonn, Germany; [4]Electron Microscopy Center Amsterdam, Department of Medical Biology, Amsterdam UMC, 1100 DD Amsterdam, The Netherlands; [5]Department of Pathology, Amsterdam UMC, University of Amsterdam, 1100 DD Amsterdam, The Netherlands

Poster number: P24

Gaucher disease (GD) and Niemann-Pick disease types A and B are lysosomal disorders with comparable by prominent presence of viable splenic lipid laden macrophages in tissues, particularly spleen. In Gaucher cells and Niemann-Pick cells respectively glucosylceramide and sphingomyelin are stored due to inherited deficiency of glucocerebrosidase (GCase) and acid sphingomyelinase (ASMase) respectively. Proteomics analysis of splenic Gaucher and Niemann-Pick storage cells

isolated by laser-captured microdissection revealed remarkable similarities. Both Niemann-Pick and Gaucher cells show increased expression of chitotriosidase, CCL18 and GPNMB. In addition, storage cells in NP-B and GD1 spleens are positive for galectin-3 and TREM2, markers of lysosomal stress.

Further immunohistochemical macrophage phenotyping further substantiated the overall similarity between Niemann-Pick and Gaucher cells, both are neither classic M1-type or M2-type but rather manifest a distinct phenotype. Lack of CD163 and mannose receptor on Niemann-Pick and Gaucher cells, but not on surrounding smaller macrophages, was observed. The observed slight overall differences in pro- or anti-inflammatory profile of NP-B and GD1 spleens seem related to differences in cellular microenvironment of storage cells. Intriguingly, differences between Gaucher and Niemann-Pick cells were noted in receptors involved in clearance of iron-containing proteins. Particularly, the transferrin receptor is more abundant in Gaucher cells than Niemann-Pick cells.

Conflict of Interest: None declared.

P25- Modelling Gaucher's Disease in African Genetic Contexts: iPSC-Derived Insights into Lysosomal and Neurodegenerative Mechanisms

Christian Hendriksz[1], Elne Conradie[1], Chris Vorster[1], Janine Schofield[2]

[1]Nort West University, Centre for Human Metabolomics, Potchefstroom Campus, Potchefstroom, South Africa; [2]Bioengineering and integrated genomics group (BIGG) CSIR Pretoria Campus, Meiring Naude Road, Brummeria, Pretoria, 0002, South Africa

Poster number: P25

Gaucher's disease (GD) is a rare autosomal recessive lysosomal storage disorder caused by pathogenic variants in *GBA1*, which encodes the enzyme glucocerebrosidase (GCase). In addition to causing monogenic GD, *GBA1* variants are among the strongest genetic risk factors for Parkinson's disease (PD), highlighting the importance of understanding how allelic heterogeneity contributes to diverse cellular pathologies. Induced pluripotent stem cell (iPSC) models have become central to dissecting these mechanisms, with both isogenic gene-edited and patient-derived systems elucidating lysosomal, mitochondrial, and proteostatic dysfunction across multiple cell types relevant to GD and PD. However, all published *GBA1* iPSC models originate from Global North populations, leaving major gaps in representation of African genetic diversity—the highest worldwide.

Conversely, an African-ancestry *GBA1* risk allele has been found in approximately half of West African PD cases. These findings suggest that unique African *GBA1* variant architectures may

modulate disease expression, yet no iPSC models exist to investigate these effects. Within the NWU Rare Disease Consortium, we have identified a Black African patient with Type 3 GD carrying the classically neuronopathic RecNciI allele in the homozygous state but with only visceral disease presenting a rare opportunity to explore genotype–phenotype dissociation.

This project aims to establish the first African-derived iPSC models of GD to illuminate mechanisms underlying neuronopathic disease in African patients and broaden global understanding of *GBA1*-related neurodegeneration. We will generate iPSC lines from Black African GD patients (beginning with the homozygous RecNciI case, followed by L444P and unaffected siblings), and differentiate these into macrophages, microglia, neurons, and midbrain organoids. Cellular models will undergo systematic assessment of lysosomal impairment, mitochondrial dysfunction, and global proteomic and metabolomic changes. Developing Africa-specific stem-cell platforms will advance equitable rare-disease research, strengthen local capacity, and potentially reveal novel therapeutic insights applicable worldwide.

Conflict of Interest: C.H., None directly connected to this abstract but potentially implicated - Co-Founder and Chief Medical officer Decentra Health as we have projects with IGA; E.C., None directly connected to this abstract but potentially implicated- lectures for -Sanofi, Astra Zeneca, Pfizer as they have products in this field; C.V., None directly connected to this poster but potentially implicated- lectures for -Sanofi, Astra Zeneca, Pfizer as they have products in this field; J.S., none declared.

P26- Interaction of GCase and GM1 ganglioside in Gaucher disease

Federico Fierli[1], Giuseppe Uras[2,3], Veronica Lentini[2,3], Sofia Koletsi[1], Anthony HV Schapira[1]

[1]Department of Clinical and Movement Neurosciences, QS Institute of Neurology, University College London, London, UK; [2]Department of Haematology, Cancer Institute, University College London, London, UK; [3]Department of Biomedical Science, University of Sassari, Sassari, Italy

Poster number: P26

Gaucher disease is a genetic disorder caused by deficiency of the lysosomal enzyme glucocerebrosidase (GCase). GCase catalyses the hydrolysis of glucosylceramide (GluCer) into glucose and ceramide. In Gaucher disease, impaired GCase activity leads to lysosomal lipid accumulation and disruption of sphingolipid metabolism.

The levels of ceramide-derived lipids in Gaucher patients remain poorly understood in the literature. Among these, the ganglioside GM1 plays a crucial role in neuronal survival through its interaction with several molecular partners, including Trk receptors, GDNF signalling, calcium homeostasis, and α-synuclein.

This project aims to further investigate the role of GM1 in the presence of GBA1 mutations.

In the first part of the study, fibroblast cell lines homozygous for GBA1 mutations (N409S and L483P) were analysed. GM1 levels and associated pathways, including endo-lysosomal and Golgi trafficking, were assessed using immunocytochemistry, Western blotting, enzymatic assays, and qRT-PCR.

Compared to WT cells, all mutant fibroblast lines showed reduced GCase activity, correlating with mutation severity. However, only the N409S homozygous fibroblasts exhibited a significant reduction in GM1 levels. This differential pattern may be explained by variations in GLB1 and

B3GALT4 protein expression, differences in recycling endosome abundance, and altered unfolded protein response (UPR) activity.

In conclusion, our findings suggest that GCase mutations may influence GM1 levels through indirect or alternative mechanisms, rather than solely through impaired ceramide availability. Future studies will focus on iPSC-derived neurons from Gaucher patients to better elucidate the impact of GM1 dysregulation on neuronal homeostasis.

Conflict of Interest: None declared.

P27- Gut Feelings in Gaucher Disease: Could the Intestinal Microbiota Shape Disease Severity?

Christine Serratrice[1], Magali Pettazzoni[2], Marc Berger[3], Nadia Belmatoug[4], Fabrice Camou[5], Yann Nguyen[4]

[1]Division of Internal Medicine for the Aged, University Hospital of Geneva, Switzerland; [2]Department of Biochemistry and Molecular Biology, University Hospital of Lyon, France; [3]Department of Biological Hematology, University Hospital of Clermont-Ferrand, France; [4]Reference Center for lysosomal Diseases, University Hospital of Paris, France;[5]Division of Internal Medicine, University Hospital of Bordeaux, France

Poster number: P27

In Gaucher Disease (GD), despite the identification of more than 450 mutations in the *GBA1* gene, the relationship between genotype and clinical presentation remains weak. This is particularly striking in type 1 Gaucher disease (GD1), which shows remarkable phenotypic heterogeneity—from asymptomatic individuals to patients with severe hematological, visceral, skeletal, and even neurodegenerative complications such as Parkinson's disease.

A growing body of evidence highlights impaired autophagy as a central mechanism in GD. Lysosomal dysfunction caused by glucocerebrosidase deficiency disrupts autophagosome–lysosome fusion, leading to autophagic blockade, macrophage inflammasome activation, and lead to accumulation of proteins such as α-synuclein. This links GD to neurodegeneration and suggests that factors modulating autophagy could critically influence disease expression.

The gut microbiota emerges as a compelling candidate modifier. This complex microbial ecosystem plays a key role in immune regulation, metabolism, and the gut–brain axis. Importantly, gut microbiota and autophagy are tightly interconnected: microbial signals and metabolites can regulate host autophagy locally and systemically, while autophagy helps maintain gut homeostasis. Dysbiosis-induced autophagy dysregulation can impair intestinal barrier integrity, promote systemic inflammation, and contribute to neuroinflammatory processes.

Although data remain scarce in lysosomal storage disorders, recent studies in Fabry disease, Sandhoff disease models, and a Drosophila model of GD suggest that altered microbiota can influence disease manifestations, immune activation, neurodegeneration, and lifespan. Together, these findings lay the groundwork for a novel hypothesis: variations in gut microbiota composition and function may modulate autophagy and inflammation, thereby contributing to the wide spectrum of clinical severity observed in GD1. Exploring this axis could open new perspectives for understanding disease heterogeneity and developing innovative, microbiota-targeted therapeutic strategies.

Within the framework of the IWGDD, a collaborative study would facilitate a more in-depth investigation of this pathophysiological mechanism.

Conflict of Interest: None declared.

P39- Impact of GBA Deficiency on Lysosomal Homeostasis and Autophagy in Human Macrophages

Veronica Lentini[1], Giuseppe Uras[1,2], David Moreno Martinez[2], Sara Lucas Del Pozo[3], Antonella Pantaleo[1], Derralynn Hughes[2]

[1]Department of Biomedical Science, University of Sassari, Viale San Pietro, Sassari, 07100, Italy; [2]Department of Haematology, UCL, London, United Kingdom; [3]Department of Clinical and Movement Neurosciences, UCL Queen Square Institute of Neurology, London, United Kingdom

Poster number: P39

Gaucher disease (GD) is an autosomal recessive lysosomal disorder resulting from mutations in the GBA gene, which cause reduced β-glucocerebrosidase activity and accumulation of glucosylceramide and related substrates within lysosomes. This metabolic defect disrupts intracellular homeostasis by impairing lysosomal function, autophagy, inflammatory signaling, and macrophage-mediated clearance, all of which are central to GD pathology. Recent studies indicate that lysosomal dysfunction and impaired processing of complex lipid cargo may alter macrophage responses to cellular stress, phagocytosis, and chronic inflammatory stimuli. Elucidating these cellular mechanisms is critical for understanding disease progression and for identifying therapeutic targets that restore degradative capacity and immune homeostasis.

Monocytes isolated from Gaucher patients were differentiated into macrophages and exposed to heat-killed HAP-1 GBA-KO cells to model the uptake of GBA-deficient material. Subsequently, cells were stimulated with lipopolysaccharide (LPS) and adenosine triphosphate (ATP) to simulate inflammasome-associated inflammatory stress. Four experimental conditions were established to assess the combined effects of phagocytosis, substrate accumulation, and inflammatory activation on macrophage biology.

Overall, Gaucher macrophages exhibited distinct alterations in lysosomal and autophagic pathways across conditions, reflecting an adaptive response to enzymatic deficiency and persistent substrate burden. Changes in lysosomal markers, autophagy regulators, and handling of phagocytosed material suggest a shift in cellular processing capacity, with GD macrophages engaging compensatory mechanisms to manage metabolic and inflammatory stress.

These preliminary findings highlight characteristic cellular responses associated with GBA deficiency and underscore the need for further investigation into how lysosomal–autophagic adaptations influence immune function and disease progression in Gaucher disease.

Conlfict of Interest: None declared.

P40- Comparative Transcriptomics Reveals Macrophage-Specific Markers Associated with Chronic GCase Loss

Emma Cuttini[1,2], Maximiliano Emanuel Ormazabal[1], Eleonora Pavan[1], Martina Cusan[1,2], Paolo Peruzzo[1], Natascha Bergamin[1], Silvia Cattarossi[1], Martina Ferro[1,2], Andrea Dardis[1]

[1]Regional Coordinator Centre for Rare Diseases, University Hospital of Udine, Udine, Italy; [2]Department of Medicine, University of Udine, Udine, Italy

Poster number: P40

Background: Macrophages play a central role in Gaucher Disease (GD) and exhibit characteristic transcriptional alterations. Unravelling their transcriptomic profile is essential to understand disease pathology and identify potential therapeutic targets.

Objectives: (1) characterize the transcriptional profile of different GD-like macrophage models. (2) validate the differential expression of selected genes putatively involved in GD pathogenesis.

Methods: Transcriptomics via the QIAseq UPXome RNA Library Kit (QIAGEN) was performed on two GD-like macrophage models obtained by differentiating: 1) wild type (WT) and GBA1 knock-out (KO) THP1 monocytic cells and 2) primary monocytes from healthy donors treated with a GCase inhibitor for 7 days. Differentially expressed genes were selected for qPCR validation by comparing the transcriptomes of these two models with a previously published dataset of iPSC-derived macrophages from a type 2 GD patient. qPCR validation was performed on these models and in two additional non-macrophagic GBA1 KO cell lines (SaOS and U87).

Results: THP1 GBA1 KO derived macrophages showed extensive transcriptional changes compared with WT (1043 up- and 1014 downregulated genes), including genes involved in pathways known to be altered in GD. Conversely, the inhibitor-based model exhibited limited transcriptional changes (7 up- and 48 downregulated genes). Three genes - CMPK2, RSAD2 and SECTM1, involved in mitochondrial biology, inflammation and macrophage polarization - were confirmed to be significantly downregulated only in THP1 GBA1 KO cells.

Conclusions: The THP1 GBA1 KO derived macrophage model recapitulates the key transcriptional features of GD, further supporting the relevance of this model. The marked differences between the two models suggest that most transcriptional alterations are driven by chronic GCase deficiency; therefore, the THP1 GBA1 KO derived macrophage model, unlike the inhibitor-based model, enables the study of long-term effects of GCase loss. Moreover, cross-model datasets comparison revealed three macrophage-specific dysregulated genes, supporting their potential as targets for future therapeutic developments.

Conflict of Interest: None declared.

P41- GBA1 Variants Influence Gut Microbiome Composition in Gaucher Disease Models

Raghu R. Sharma[1], Chris Staley[2], Subbaya Subramanian[2], Ying Sun[3], **Reena V. Kartha[1]**

[1]Center for Orphan Drug Research, Department of Experimental and Clinical Pharmacology, College of Pharmacy, University of Minnesota, Minneapolis, MN, USA – 55455; [2]Department of Surgery, Medical School, University of Minnesota, Minneapolis, MN, USA – 55455; [3]Division of Human Genetics, Cincinnati Children's Hospital Medical Center; Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, OH, USA - 45229

Poster number: P41

The gut microbiome plays a vital role in maintaining metabolic and immune homeostasis. Microbiome dysbiosis has been implicated in various inflammatory and neurological disorders. Gaucher disease (GD), caused by GBA1 mutations, involves systemic and neurological features

with an increased risk of Parkinson's disease. Gut dysbiosis has been linked to PD; however, its contribution to neuroinflammation and neurodegeneration in the context of GBA1 variants remains under explored. Our objective is to longitudinally characterize alterations in the gut microbiome in two neuronopathic GD mouse models, 4L/PS-NA (Gba1-V394L/PS-NA) and 9H/PS-NA (Gba1-D409H/PS-NA), generated by combining GCase point mutations with reduced saposin levels. These models exhibit severe glucosylceramide accumulation across multiple organs, simulating GD-associated neurodegeneration. Our objective is to longitudinally characterize changes in the gut microbiome and their potential relationship to neurodegeneration, compared with age-matched wild-type (WT) mice. Fecal samples were collected every 4 weeks up to 24 weeks, and microbiome profiles were analyzed using 16S rRNA sequencing. Preliminary analysis of samples collected at 4 and 8 weeks (disease onset stage) revealed minimal temporal variation in the fecal microbiome within each strain, but significant compositional differences among strains (analysis of similarity, $R = 0.94$, $P < 0.001$). Relative abundances of Oscillospiraceae (not further classified) were significantly greater in 9H/PS-NA, relative to WT (Kruskal-Wallis $P = 0.007$). In comparison, Odoribacter abundances were significantly greater in 4L/PS-NA than in WT ($P < 0.001$). The finding of significant compositional differences in the gut microbiome among the mutant strains and WT mice suggests that GBA1 variants may directly influence the gut microbial community structure. These observed alterations, or dysbiosis, may contribute to systemic inflammation and neurodegeneration in GD. Further analysis of samples collected until 24 weeks is underway. Taken together, this data will provide information on longitudinal age-related alterations in the gut microbiome that correlate with GD progression.

Conflict of Interest: R.K., has received IIS research grants from Sanofi, Pfizer, Takeda Pharmaceuticals and education grant from Sanofi. All other authors have no COI to disclose.

Therapies in Gaucher Disease (Giusto Room)

P52- Medication Switch in Type 1 Gaucher Disease- clinical and patient perspective.

Mia Giles[1], Asmaa Alzuabi[1], Mairead Jones[1], Karolina M. Stepien[1]

[1]Salford Royal Hospital, Northern Care Alliance NHS Foundation Trust

Poster number: P52

Background: Gaucher disease type 1 (GD1) is caused by pathogenic variants in the GBA1 gene. Available therapies include three enzyme replacement therapies (ERT) and two substrate reduction therapies (SRT). This study explored the patient perspective for switching medication in GD1.

Methods: A retrospective review of all GD1 patients' demographics, clinical, nursing and therapy-related outcomes at one tertiary centre.

Results: 28 patients were included (median age at diagnosis 15 years, range 0-54; 53.8% males). Primary reasons for medication switch at any time included the 2009 Cerezyme shortage (35.7%), oral preference (64.3%) and poor tolerance (14.3%); with needle and infusion anxiety, depression and non-adherence due to insufficient response affecting 10.7%, 7.1% and 3.6% respectively. Of the 26 (30.8% childhood-onset, 23.1% adult-onset) treated with Cerezyme; 53.9% reported satisfaction; 11.5% who found dramatic energy improvement. 11.5%

faced intravenous/ port access difficulties and associated emotional stress, 3.8% suffered from osteodynia. Adherence was positive, with non-adherence linked to the 2009 supply crisis prompting therapy switches. Twenty-two received Velaglucerase (38% childhood-onset) with 45.5% reporting stability and positive adherence. However, 36.4% cited intravenous administration as inconvenient; 22.7% found treatment insufficient (osteodynia). Non-adherence was due to supply shortages. Seven patients received Miglustat; 57.1% reported adverse effects, which led to poor adherence. Among 23 patients treated with Eliglustat (50% childhood-onset), 70.8% experienced symptomatic improvement, 12.5% no improvement, 8.7% chronic osteodynia, anxiety or GD1 exacerbations and 4.3% ceased due to intolerability. **Conclusions:** Oral versus intravenous medication route drove medication switch in the vast majority. Notably, the tolerability of these medications and accommodating to patients' personal lives played a significant role in the decision to switch therapies. Future research is vital to appreciate the critical nature of autonomy in chronic metabolic disease. The patients' perspective should be considered when the therapy is prescribed, as it may impact on their compliance.

Funding: The work has been supported with an educational grant from Takeda

Conflict of Interest: None declared.

P53- Trial in Progress: GALILEO-3, a Phase 3 Registrational Trial of avigbagene parvec (FLT201) Gene Therapy Candidate in Patients with Gaucher Disease type 1

Reena Sharma[1], Shoshana Revel-Vilk[2,3], Ozlem Goker-Alpan[4], Ida Schwartz[5], Pilar Giraldo[6], Pamela Foulds[7], Philip Yin[7], Dan Wolf[7], Simon Flynn[7], Derralynn Hughes[8,9]

[1]Salford Royal Hospital, United Kingdom; [2]Gaucher Unit, The Eisenberg R&D Authority, Shaare Zedek Medical Center, Jerusalem, Israel; [3]Faculty of Medicine, Hebrew University, Jerusalem, Israel; [4]Lysosomal and Rare Disorders Treatment Center, Virginia, USA; [5]Hospital de Clinicas de Porto Alegre, Brazil; [6]Hospital Quironsalud de Zaragoza, Spain; [7]Spur Therapeutics, Stevenage, United Kingdom; [8]Royal Free Hospital, London, United Kingdom; [9]University College London, United Kingdom

Poster number: P53

Avigbagene parvec (FLT201) is a liver-directed gene therapy candidate designed to overcome the limitations of enzyme replacement therapy (ERT) and substrate reduction therapy (SRT) for patients with Gaucher disease type 1 (GD1) with a single infusion. It leverages a rationally designed liver-selective adeno-associated virus capsid (AAVS3) to deliver a transgene encoding GCase85, a novel, engineered GCase variant with enhanced stability. This approach enables continuous systemic and intracellular expression of GCase85, providing sustained enzyme exposure beyond what is achievable with ERT.

GALILEO-3 (EU CT 2025-520765-50) is an open label, non-randomized, global, multicenter, phase 3 study designed to evaluate the safety and efficacy of FLT201 in adults with GD1. The study will enroll approximately 45 adults with GD1 who have been on stable ERT/SRT treatment for at least 2 years. Participants will receive a single IV infusion of FLT201 at a dose of 4.5 x 1011 vg/kg, discontinue ERT/SRT treatment after week 4, and will be followed for a period of 5 years. A primary analysis will occur at Week 52 with the option for an interim analysis to occur at Week 24 and a final analysis at the end of study. The primary endpoint for the study is the proportion of participants with stable hemoglobin concentration (decrease from baseline of no more than 1.5 g/dL) at Week 52. Key secondary efficacy endpoints include change from baseline in lyso-Gb1 levels and the proportion of participants with stable platelet count, spleen volume, and

liver volume at Week 52. Further endpoints will evaluate safety, bone health, and various patient reported outcome measures (PROMs) to assess quality of life, Gaucher disease severity (DS3), and fatigue. GALILEO-3 is intended to support the registration of FLT201 for the GD1 population.

Conflict of Interest: R.S. has received honoraria for consulting from Amicus, Sanofi, Chiesi, Ultragenyx, Immedica and Takeda. S.R-V. has received research support, honoraria for speaking and travel support from Takeda, Sanofi and Pfizer; honoraria for advisory board participation from Takeda. O.G-A. has received honoraria for advisory board participation from Spur, Prevail/Lilly and Sanofi; honoraria for speaking and research support from Sanofi. I.S. has received honoraria for speaking and travel support from Sanofi and Takeda. P.F., D.W., and S.F. are employees of Spur Therapeutics. P.Y. is a former employee of Spur Therapeutics. D.H. has received honoraria for speaking and advisory board participation from Takeda, Sanofi, Amicus and Chiesi; honoraria for advisory board participation from Spur, Uniqure, Idorsia, Medpace and Biomarin; research support from Chiesi.

P54- Development and Multi-Step Purification of a Novel Recombinant Glucocerebrosidase (GCase-7) from a Stable Human Cell Line for Gaucher Disease Replacement Therapy

Lílian Louise Souza Figueiredo[1], Frederico Guilherme Freitas Lobão Rodrigues Gomes[1], Alline Cristina de Campos[2], Suely Vilela Sampaio[3], Guilherme Rabelo Coelho[3], Adelia Cristina Oliveira Cintra[3], Thiago Abrahão Silva[3], Velia Siciliano[4], Ron Weiss[5], Aparecida Maria Fontes[1]

[1]Department of Genetics, Ribeirão Preto Medical School – University of São Paulo, Ribeirão Preto, 14049-900, SP, Brazil; [2]Department of Pharmacology, Ribeirão Preto Medical School - University of São Paulo, Ribeirão Preto,14049-900, SP, Brazil; [3]Department of Clinical Analyses, School of Pharmaceutical Sciences of Ribeirão Preto, University of São Paulo, Ribeirão Preto, 14049-900, SP, Brazil; [4]Istituto Italiano di Tecnologia, Center for Advanced Biomaterials for Healthcare, Via Morego, 30, Genova, Italy; [5]Synthetic Biology Center, Department of Biological Engineering, Massachusetts Institute of Technology, 77 Massachusetts Ave, Cambridge, Massachusetts, EUA.

Poster number: P54

Gaucher Disease (GD), an autosomal recessive lysosomal storage disorder caused by deficient glucocerebrosidase (GCase) activity, is primarily treated with enzyme replacement therapy (ERT). To develop a more efficient production platform, we previously applied *in silico* directed evolution and synthetic biology to develop GCase-7, a novel variant with seven *missense* mutations in its signal peptide. This study reports the establishment of a stable human cell line (293FT) producing GCase-7 using lentiviral transduction (titer: 1.68×10^7 VP/mL). A high-producer clone demonstrated a four-fold increase in specific intracellular activity (241.10 ±19.83 nmol/mg/h) and a seven-fold increase in secreted activity (27.48 ± 3.00 nmol/mL/h) compared to wild-type cells. To isolate the recombinant enzyme, we implemented a multi-step purification strategy. Cell lysates were initially concentrated using a 30-kDa centrifugal filter, achieving a 1.7-fold enrichment in specific activity. Subsequent purification by anion-exchange (QXL) and cation-exchange (SP) chromatography at neutral pH resulted in minimal retention of GCase activity, which was predominantly recovered in the flow-through fractions. This suggests either a suboptimal interaction under the conditions used or potential column overload during initial screenings. Hydrophobic interaction chromatography (HIC) (Phenyl Sepharose) successfully bound and eluted enzymatically active fractions, as confirmed by specific inhibition with conduritol B epoxide. Reverse-phase (C18) chromatography resulted in loss of activity. Scale-up of HIC confirmed enzyme recovery. SDS-PAGE analysis of active fractions revealed bands at the expected molecular weight. Current efforts are focused on the detailed

characterization of these fractions by mass spectrometry to confirm GCase-7 identity and optimize yield. Parallel purification from culture supernatant is underway to improve recovery. This work demonstrates the feasibility of producing functional GCase-7 from a transgenic human cell system and outlines a purification pathway toward therapeutic development.

Acknowledgements: Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil (CAPES) - Finance Code 001, Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP), Fundação de Apoio ao Ensino, Pesquisa e Assistência (FAEPA-USP).

Conflict of Interest: None declared.

P55- A Novel dual Mode of Action for a Glucosylceramide Synthase Inhibitor as a Treatment for Gaucher Disease

Aidan Gill[1], Laura López de Frutos[1]

[1]Azafaros B.V., Leiden NL

Poster number: P55

Introduction: Gaucher disease is a caused by pathogenic variants in *GBA*, leading to deficient activity of glucocerebrosidase. This results in the accumulation of glucosylceramide within macrophages, causing various systemic manifestations including hepatosplenomegaly, bone lesions, anaemia, and neurological complications in certain subtypes. Current treatment strategies include enzyme replacement therapy (ERT) and substrate reduction therapy (SRT), with the latter aimed at decreasing the synthesis of a range of glycosphingolipids.[1]
Rationale for a New GCS Inhibitor: While existing SRTs, like eliglustat and miglustat, have demonstrated efficacy, limitations persist: some patients exhibit suboptimal responses, particularly those with advanced disease or specific genotypes; current inhibitors may cause adverse effects, including gastrointestinal discomfort and peripheral neuropathy, in individuals with CYP2D6 polymorphisms and existing SRTs have limited efficacy in neuronopathic Gaucher disease due to poor blood-brain barrier penetration.
Potential Benefits: A novel glucosylceramide synthase inhibitor could offer significant advantages: Dual enzyme inhibition, acting on GCS and NLGase promotes a rebalancing of the homeostasis for ceramide metabolism rather than merely blocking the breakdown pathways at a different point; the inhibition of NLGase may have a positive impact on lysosomal pH regulation. Improving selectivity could reduce dose and improve safety margins and may enhance therapeutic outcomes; optimising pharmacokinetics and reducing drug-drug interactions and off-target interactions could make the therapy safer, especially for patients with comorbid conditions.[2] Current GCS inhibitors have activity on the systemic or visceral manifestations associated with all forms of Gaucher disease, but the greatest unmet need is for molecules that can cross the BBB which may provide therapeutic options for neuronopathic forms.
Conclusion Nizubaglustat, a new glucosylceramide synthase and NLGase inhibitor, has potential to address the need for improved efficacy, safety, and CNS penetration. This could address current treatment gaps, offering hope for better outcomes in non-neuronopathic and neuronopathic GD patients.

References:
[1]Mehta A, (2006) Epidemiology and natural history of Gaucher's disease, European Journal of Internal Medicine, Vol 17, Supplement p S2-S5 doi.org/10.1016/j.ejim.2006.07.005.
[2]Pacquet-Luzy C., et al. (2024) First-in-human single-dose study of nizubaglustat, a dual inhibitor of ceramide glucosyltransferase and non-lysosomal glucosylceramidase: safety, tolerability,

pharmacokinetics, and pharmacodynamics of single ascending and multiple doses in healthy adults, Mol. Genet. Metab., 141 (1), doi.org/10.1016/j.ymgme.2023.108113

Conflict of Interest: Authors are employees of or employed by Azafaros

P56- A phase 2 PoC study to evaluate the efficacy of nizubaglustat on the visceral and systemic symptoms in patients with neuronopathic Gaucher Disease

Laura Lopez de Frutos[1], Aidan Gill[1], An Rykx[1], Dominique Nijkamp[1], and Chris Freitag[1]

[1]Azafaros B.V., Leiden NL

Poster number: P56

Nizubaglustat is an experimental oral compound capable of crossing the blood-brain barrier, intended for the treatment of neurodegenerative lysosomal diseases. Its dual mechanism of action, inhibiting glucosylceramide synthase and non-lysosomal glucocerebrosidase, allows it to aOect two distinct pathophysiological pathways to inhibit disease progression.

A phase 2 study conducted in Brazil (NCT05758922) demonstrated a favorable safety profile in patients with NPC and GM2, without reports of gastrointestinal adverse events typically associated with compounds with a similar mode of action. While the study was not intended to demonstrate clinical eOicacy, it revealed encouraging data regarding clinical signs of ataxia and seizures when contrasting treated patients in a natural history study (NCT05109793).

A phase 3 pivotal study to evaluate eOectiveness in GM1/2 Gangliosidoses and NPC was developed and initiated in July 2025 (NCT07054515).

It is clear that there remains a significant unmet need in nGD patients.

The neurological symptoms of nGD may take many months to years to change, however, to be an eOective monotherapy for nGD the medication must quickly address the visceral symptoms. We propose a Phase 2 PoC protocol that is divided in two. The initial assessment of Platelet count, Haemoglobin and Spleen size over 6 months is followed by an 18-month extension assessing the neurological symptoms that the patients are experiencing at baseline and any that develop during that period. Natural History publications have guided our choices of neurological assessments.

The main inclusion criteria consist of: genetic diagnosis (homozygous L483P); a baseline age over 4 years and at least two neurological symptoms described on the mSST. Patients weighing less than 10 Kg, with other confounding diseases, using diOerent investigational drugs, or who are receiving Enzyme Replacement Therapy are excluded. Other prescribed or OTC medications are permitted.

The study plans to recruit about 20 participants from up to 3 sites.

Conflict of Interest: Authors are employees of or employed by Azafaros

P57- Results of Long-Term Use of Maintenance Regimen of Enzyme Replacement Therapy for Gaucher Disease

Rodion Ponomarev[1], Rolanda Chavynchak[1], Elena Sysoeva[1], Albina Belyakova[1], Margarita Galimova[1], Yulia Chabaeva[1], Sergey Kulikov[1], Elena Lukina[1]

[1]National Research Center for Hematology, Moscow, Russia

Poster number: P57

Introduction: In the Russian Federation, ERT is administered to 295 adult patients with Gaucher disease (accounting for 92% of patients receiving pathogenetic therapy), with the proportion of patients on a maintenance ERT regimen being 55%. By 2025, the median duration of the maintenance ERT regimen reached 8.8 years, highlighting the need to evaluate the long-term outcomes of this treatment approach.

Objective: To assess the efficacy of ERT in a maintenance regimen for patients with Gaucher disease.

Materials and Methods: The study included 163 adult patients with type 1 Gaucher disease who were switched to a maintenance treatment regimen (recombinant glucocerebrosidase 15-20 U/kg once a month) between 2015 and 2025. The dynamics of key disease activity markers were assessed using averaged regression dependencies with generalized linear models.

Results and Discussion: At the time of analysis, long-term maintenance ERT was assessed as effective in 134 patients (82.3%). In this patient group, the Gaucher disease severity score index remained stable. Twenty-nine patients (17.7%) were switched back to the standard ERT regimen due to increased disease activity (median duration of maintenance ERT – 61.4 months), manifested by a decrease in hemoglobin and platelet levels, an increase in spleen size and the Gaucher disease severity score index. Factors associated with an insufficient response to the maintenance ERT regimen are a Gaucher disease diagnosis age of <20 years (p=0.0063) and an age at switching to the maintenance ERT regimen of <35 years (p=0.0013). In contrast, hemoglobin and platelet levels, disease severity score index, and the degree of splenomegaly at the time of switching to the maintenance regimen did not show a significant association with the effectiveness of subsequent therapy.

Conclusion: Maintenance regimen ERT in adult patients with Gaucher disease is characterized by high efficacy, manifesting as stabilization of disease activity parameters in the vast majority of patients.

Conflict of Interest: None declared.

P58- Next-Generation Enzyme Replacement Strategies for Gaucher Disease

Pau Sarlé[1,2], Eddi Pradas[1,2], Pablo Castillo-Sánchez[2], Sebastián Tanco[1], Mercedes Arrúe-Gonzalo[2], Pol Rodriguez-Carreras[2], Clara Carnicer-Caceres[3], Laura Castillo-Ribelles[3], Maria Camprodon[4], Maria Medel[5], Maria Jesus Vicent[5], Marta Artola[6], Marta Martínez-Vicente[2], Julia Lorenzo[1]

[1]Protein Engineering and Nanomedicine Group (IBB). Universitat Autònoma de Barcelona (UAB), Spain; [2]Neurodegenerative Diseases Group, Vall d'Hebron Research Institute (VHIR), Barcelona, Spain; [3]Biochemistry Service, Vall d'Hebron Hospital, Barcelona, Spain; [4]Rare disaeaseVall d'Hebron Hospital, Barcelona, Spain; [5]Polymer Therapeutics Lab. Centro de Investigación Príncipe Felipe (CIPF), Valencia, Spain; [6]Department of Medical Biochemistry, Leiden Institute of Chemistry, Leiden University, Leiden, The Netherlands.

Poster number: P58

Gaucher disease (GD), one of the most common lysosomal storage disorders (LSD), is caused by a deficiency in the β-glucocerebrosidase (GBA) enzyme. Impaired GBA activity leads to accumulation of glucosylceramide and glucosylsphingosine within the lysosomes. Enzyme

replacement therapy (ERT) has revolutionized the management of several LSDs over the last few decades, including GD. Periodic intravenous administration of active GBA has proven effective in reversing most visceral manifestations of the disease. However, there are important drawbacks associated with ERT, such as GBA poor stability and inactivation in the bloodstream leading to high and frequent doses. Moreover, the current ERT for GD is ineffective in treating bone disease and neurological manifestations.

For that reason, there is a need to optimize it and improve its biodistribution. To overcome these challenges, we developed an optimized GBA production in a mammalian expression system through the incorporation of specific additives. This strategy yielded two cost-effective GBA glycoforms with catalytic properties comparable to those commercially available. To further enhance their therapeutic potential, all GBA variants were nanoconjugated to a biocompatible polymer, leading to improved stability and biodistribution without compromising enzymatic activity. The efficacy of these enzymes and their nanoconjugates has been validated both in vitro using a GBA KO cellular model and in vivo using GBA mutant mice models, demonstrating superior internalization and biodistribution compared with the standard treatment.

Overall, our results provide proof of concept for a next-generation ERT approach that combines reduced manufacturing costs with improved therapeutic efficacy, offering a promising avenue for more accessible and effective management of Gaucher disease.

Conflict of Interest: None declared.

P59- Bone mineral density improvements in velaglucerase alfa-treated patients with Gaucher disease: Real-world evidence from the Gaucher Outcome Survey (GOS)

Zimran A,[1,2] Botha J,[3] Eastell R,[4] Ficicioglu C,[5,6] Finkelman R.D,[7] Frydman D,[1] Giraldo P,[8,9] Göker-Alpan Ö,[10] Kishnani PS,[11] Lau H,[12] Ruhrman-Shahar N,[13] Hughes D.A.[14]

[1]Gaucher Unit, Shaare Zedek Medical Center, Jerusalem, Israel; [2]Faculty of Medicine, Hebrew University, Jerusalem, Israel; [3]Takeda Pharmaceuticals International AG, Zurich, Switzerland; [4]Academic Unit of Bone Metabolism, University of Sheffield, Sheffield, United Kingdom; [5]Division of Human Genetics and Metabolism, The Children's Hospital of Philadelphia, Philadelphia, PA, USA; [6]Perelman School of Medicine at the University of Pennsylvania, PA, USA; [7]Takeda Development Center Americas, Inc., Cambridge, MA, USA; [8]Translational Research Unit, IIS Aragon, Zaragoza, Spain; [9]Hospital Quironsalud, FEETEG, Zaragoza, Spain; [10]Lysosomal and Rare Disorders Research and Treatment Center, Fairfax, VA, USA 11. Division of Medical Genetics, Department of Pediatrics, Duke University Medical Center, Durham, NC, USA; [12]Internal Medicine, Yale University, Weston, CT, USA; [13]The Raphael Recanati Genetics Institute, Rabin Medical Center - Beilinson Hospital, Petah Tikva, Israel; [14]LSD Unit, Royal Free London NHS Foundation Trust, University College London

Poster number: P59

Osteopenia and osteoporosis are common in Gaucher disease (GD), monitored with bone mineral density (BMD) measurements, and are expressed as Z-scores to quantify deviations from the average BMD of the age and gender-matched normal population. However, the lack of standardized protocols for BMD assessment, including image analysis, poses significant challenges in the reliable collection, interpretation, and comparison of these data, limiting clinical utility. This analysis presents findings from the Gaucher Outcomes Survey (GOS) registry (NCT03291223), which collects real-world data on GD treatments, including long-term BMD assessments. Between December 2010 and February 2024, 2156 patients were enrolled, with

401 receiving velaglucerase alfa only. BMD lumbar spine (LS) Z-scores were assessed in 34 adult GD1 patients (16 male, 18 female) from five countries who received velaglucerase alfa only (dose range: 15–90 U/kg every 2 weeks) for at least 8 years. At velaglucerase alfa initiation (baseline), mean (SD) age was 42.9 (15.8) years and the mean (95% CI) BMD LS Z-score was -1.0 (-1.44; -0.61) range -2.8 to 1.6; 13 patients had osteopenia and 8 had osteoporosis. Three patients had undergone a total splenectomy (baseline mean BMD LS Z-score -1.2 [-3.73; 1.27] range -2.3 to -0.3). After 8 years of treatment, the mean BMD LS Z-score for 34 patients improved to -0.5 (-0.88; -0.02), representing an average increase of 0.6 (0.33; 0.82), with similar improvements observed in both males and females. A critical observation from this analysis was the substantial variability in BMD data across study sites, which compromised the ability to make reliable scientific and clinical comparisons. Despite the small sample size, these findings suggest that velaglucerase alfa contributes to meaningful BMD improvements in GD1 patients over time. Moving forward, the development of standardized protocols for BMD assessment is essential to generate more reliable data and optimize patient outcomes.

Funding: GOS is funded by Takeda Pharmaceuticals International AG, Zurich, Switzerland.

Acknowledgements: Under the direction of the authors, Isobel Lever, PhD, CMPP employee of Envision Catalyst, an Envision Medical Communications agency, a part of Envision Pharma Group, provided writing assistance for this publication. Editorial assistance in formatting, proofreading, copy editing, and factchecking was also provided by Envision Catalyst. Takeda Development Center Americas Inc., Lexington, MA, USA, provided funding to Envision Catalyst, for support in writing and editing this abstract.

Conflict of Interest: A.Z., received honoraria from BioEvents, Pfizer, and Takeda; and is founder and current CMO of AGYANY Pharma Ltd. J.B., is an employee of Takeda Pharmaceuticals International AG and holds stock and/or share options in Takeda Pharmaceutical Company Ltd. R.E., receives consultancy funding from AstraZeneca, Biocon, CL Bio, Cureteq, Grünenthal, Immunodiagnostic Systems, Samsung, Sandoz, Takeda, Theramex, and UCB Pharma; participated in meeting presentations for Alexion, Amgen, Pharmacosmos, Radius Health, and UCB Pharma; received travel funding from CL Bio and Samsung; and received grant funding from Alexion, CL Bio, and osteolabs. C.F., served as an advisor or consultant for Acer Therapeutics, AVROBIO, Chiesi, Horizon Therapeutics, Sanofi Genzyme, Takeda, and Travere Therapeutics; received grants for clinical research from Denali Therapeutics, JCR Pharmaceuticals Co., Ltd., Jnana Therapeutics, Passage Bio, REGENXBIO, Sanofi Genzyme, Synlogic Therapeutics, Takeda, and Travere Therapeutics. R.D.F. is a former employee of Takeda Development Center Americas, Inc., and holds stock and/or share options in Takeda Pharmaceutical Company Ltd, and works as a consultant to Takeda Development Center Americas, Inc. D.F. reports no conflict of interest. P.G. received fees for presentations, advisory boards, and grants for research projects from Alexion, Amicus Therapeutics, Pfizer, Sanofi Genzyme, and Takeda. Ö.G.-A. served on advisory boards and received consulting fees from 4DMT, Amicus Therapeutics, Sangamo Therapeutics, Sanofi Genzyme, and Takeda; has research contracts with 4DMT, Amicus Therapeutics, AVROBIO, Freeline, Genentech, Protalix, Sangamo, Sanofi Genzyme, and Takeda; and has participated in speaker bureaus for Sanofi Genzyme and Takeda. P.S.K. received research/grant support from Sanofi Genzyme and Takeda; received consulting fees and honoraria from Sanofi Genzyme and Takeda; and is a member of the Gaucher Disease Registry advisory board for Sanofi Genzyme and a member of the advisory board for Takeda. H.L. received consulting fees from Actelion, Pfizer, Sanofi Genzyme, and Takeda; and research grants from Amicus Therapeutics, BioMarin, Pfizer, Protalix, Sangamo, Sanofi Genzyme, Takeda, and Ultragenyx. N.R.-S. received consulting fees and honoraria from Sanofi Genzyme, Pfizer and Takeda. D.A.H. received consulting fees and fees for non-CME/CE services from Genzyme, Sanofi, and Takeda.

P60- Long-Term (Up to 18 Years) Efficacy and Safety of Eliglustat in Patients with Gaucher Disease Type 1: A Single-Center Retrospective Follow-Up

Margarita Galimova[1], Rolanda Chavynchak[1], Elena Sysoeva[1], Rodion Ponomarev[1], Elena Lukina[1]

[1]National Medical Research Center for Hematology, Department of Orphan Diseases, Moscow,Russian Federation

Poster number: P60

Background: Enzyme replacement therapy (ERT) is highly effective for Gaucher disease type 1 (GD1) but imposes a lifelong burden of intravenous infusions. Eliglustat, an oral substrate reduction therapy (SRT), demonstrated efficacy and safety in phase 2–3 trials. However, data on its very long-term outcomes in real-world settings remain limited.

Aim: To evaluate the long-term durability of response, safety, and treatment adherence in patients with GD1 who continued eliglustat therapy for up to 18 years after completing the clinical trials.

Methods: This single-center retrospective study included 17 adult patients (10F/7M) with GD1 who completed the international phase 2–3 clinical trials (2006-2015) and remained on eliglustat. Ten were treatment-naïve, seven switched from ERT (median ERT duration: 191 months). All had achieved therapeutic goals by trial completion. We analyzed clinical, laboratory (hematological, biochemical, immunoglobulin), radiological (abdominal ultrasound), and MRI (femurs) parameters during long-term follow-up (2024-2025).

Results: After a median total eliglustat exposure of ~18 years, 16 of 17 patients (94%) sustained all therapeutic goals. Hematological parameters remained stable without cytopenia. Median total cholesterol and ferritin levels were within normal range. Polyclonal hypergammaglobulinemia persisted in 2/17 patients. Organomegaly was minimal: median spleen volume was 1.7x ULN (range 1-4.7), median liver volume was 1.1x ULN (1-1.5); only one patient had clinically significant splenomegaly. Bone marrow infiltration on MRI was absent or residual, with no new osteonecrosis. Critically, all 17 patients maintained 100% adherence to oral therapy.

Conclusion: This study provides the longest follow-up data for eliglustat in GD1, demonstrating durable efficacy and safety over 18 years. Oral SRT with eliglustat successfully maintains treatment goals in most of the patients, offering a sustainable and effective long-term alternative to intravenous ERT, with excellent adherence.

Acknowledgements: we extend our gratitude to Genzyme/Sanofi for providing treatment to our patients with GD1 under the humanitarian aid program.

Conflict of Interest: None declared.

P61- Impact of avigbagene parvec (FLT201) on markers of bone health in adults with Gaucher Disease Type 1

Pilar Giraldo[1], Ozlem Goker-Alpan[2], Ida Schwartz[3], Reena Sharma[4], Ravi Kamath[5], Pamela Foulds[6]

[1]Hospital Universitario Quironsalud, Zaragoza, Spain; [2]Lysosomal and Rare Disorders Treatment Center, Virginia, USA; [3]Hospital de Clinicas de Porto Alegre, Brazil; [4]Salford Royal Hospital, United Kingdom; [5]Fairfax Radiological Consultants, Virginia, USA; [6]Spur Therapeutics, Stevenage, United Kingdom

Poster number: P61

Bone involvement is a major contributor of morbidity in Gaucher disease even after years of therapy with ERT or SRT. Patients continue to experience bone marrow infiltration and reduction in bone marrow density, with debilitating pain and a major impact on quality of life.

FLT201 is an investigational AAV gene therapy for Gaucher disease type 1 (GD1). A single infusion of FLT201 has the potential to deliver continuous, durable endogenous expression of GCase eliminating the need for chronic treatment with ERT or SRT. The increased stability of GCase85 delivered by FLT201 provides sustained exposure leading to increased tissue uptake, which could improve bone outcomes.

GALILEO-1 enrolled adults with GD1 on stable treatment with either ERT or SRT for at least two years. Participants received a single IV infusion of FLT201 at 4.5×10^{11} vg/kg. Four patients treated with FLT201 came off background ERT/SRT and demonstrated improvement or maintenance of markers of bone health.

DEXA improved or remained in the normal range (Z score) in all 4 participants. One patient, who was stable at study entry in hemoglobin, platelets, and organ volume, had a clinically relevant improvement in lumbar spine Z-score from -3.5 to -2.5 after receiving FLT201. This same patient had Z score improvements in the femur from osteopenic ranges to normal.

Bone marrow burden improved substantially in one patient. Patient reports of bone pain and pain interference improved. Levels of osteocalcin and bone specific alkaline phosphatase declined during the course of immunosuppression but rebounded to baseline (normal) levels by Month 6 post FLT201, demonstrating the reversible nature of the effect.

Overall, FLT201 has demonstrated the potential for improvement in bone health, a difficult-to treat-organ in GD1.

Conflict of Interest: P.G. no disclosures. O.G-A. has received honoraria for advisory board participation from Spur, Prevail/Lilly and Sanofi; honoraria for speaking and research support from Sanofi. I.S. has received honoraria for speaking and travel support from Sanofi and Takeda. R.S. has received honoraria for consulting from Amicus, Sanofi, Chiesi, Ultragenyx, Immedica and Takeda. R.K. has received honoraria for consulting from Sanofi and Takeda; honoraria for speaking from Sanofi. P.F. is an employee of Spur Therapeutics.

Gaucher Disease Clinical Spectrum (Zodiaco Room)

P67- Triumphs and Challenges in Managing Gaucher's Disease in Kenya

Phoebe Wamalwa[1], Lucy Mungai[1]

[1]Kajiado County Referral Hospital; Kenyatta University; Pediatric Endocrine Society Kenya

Poster number: P67

Background: Gaucher's disease, a rare autosomal recessive lysosomal storage disorder caused by glucocerebrosidase deficiency, remains largely underdiagnosed in sub-Saharan Africa due to limited awareness, inadequate diagnostic capacity, and the prohibitive cost of enzyme replacement therapy (ERT). In Kenya, these barriers are compounded by geographical inequities, a shortage of trained specialists, and dependence on overseas laboratories for confirmatory testing. This report highlights the diagnostic and therapeutic journeys of four

pediatric Gaucher's disease cases, illustrating both the systemic challenges and significant progress achieved in managing rare diseases within resource-limited settings.

Case Presentations:

Case 1: A 1-year-8-month-old child presented with severe anemia, bleeding tendencies, and massive splenomegaly after multiple misdiagnoses, including visceral leishmaniasis. Enzyme assay confirmed glucocerebrosidase deficiency and GBA1 mutations; ERT was initiated after regulatory delays, resulting in full recovery and normalization of growth within eight months.

Case 2: A 1-year-3-month-old girl with hepatosplenomegaly, severe anemia, and recurrent respiratory infections experienced diagnostic delays due to repeated consultations and herbal treatments.

Case 3: A 2-year-old girl with chronic abdominal distension, poor growth, and multiple fractures was mismanaged for tuberculosis before Gaucher's disease was confirmed.

Case 4: A 6-year-old from coastal Kenya with longstanding anemia and abdominal swelling was initially treated for malnutrition; evaluation for lysosomal storage disorders revealed Gaucher's disease. Three of these patients are currently receiving ERT at different centers across Kenya.

Challenges and Triumphs: Key challenges included diagnostic delays, overlap with endemic diseases, high treatment costs, and fragile supply chains. Success was realized through multidisciplinary teamwork, international partnerships, and enhanced clinician training.

Conclusion: Gaucher's disease can be effectively diagnosed and treated in low-resource settings through sustained advocacy, capacity building, and integration of rare diseases into national health strategies.

Conflict of Interest: None declared.

P68- Growing Awareness of Gaucher Disease Is Increasing the Annual Volume of Diagnostic Samples

Tama Dinur[1], Ari Zimran[1,2], Elena Schulman[1], Dafna Frydman[1], Michal Becker-Cohen[1], Shoshana Revel- Vilk[1,2]

[1]Gaucher Unit, The Eisenberg R&D Authority, Shaare Zedek Medical Center, Jerusalem; [2]The Faculty of Medicine, Hebrew University, Jerusalem, Israel

Poster number: P68

Introduction: Our earlier cohort study (2014–2021) demonstrated that lyso-Gb1 measurement on dried blood spots (DBS), combined with *GBA1* sequencing, provides highly sensitive and specific diagnostic performance and supports its use as a first-line test for Gaucher disease (GD). We now present updated data from a contemporary cohort and compare diagnostic patterns with our earlier experience.

Methods: DBS samples collected between 2022 and 2025 were analyzed for lyso-Gb1 using the previously described protocol, alongside *GBA1* sequencing for all individuals. Clinical data, referral indications, and genotypes were extracted from the Gaucher Unit registry and compared across diagnostic groups and GD severity types.

Results: Among 320 individuals tested, 47 (14.7%) were diagnosed with GD. Patients with GD were younger than those without GD (median age 19 vs. 36 years; $p < 0.001$), and children (≤18 years) accounted for 42.6% of new diagnoses. Lyso-Gb1 levels were markedly higher in individuals with GD compared with those without GD (168.0 ng/mL [9.4–631.0] vs. 6.3 ng/mL [1.8–13.2]; $p < 0.001$). Referral indications differed significantly ($p = 0.003$), with clinical suspicion and family history being the most common among confirmed cases. Prenatal screening accounted for 6.4% of diagnoses.

Stratification by GD type showed expected biological gradients. Patients with mild type I disease ($n = 33$) had lower median lyso-Gb1 levels (133.0 ng/mL [9.4–631.0]) compared with severe type I cases ($n = 13$; 342.0 ng/mL [23.6–611.0]). Severe cases were diagnosed at a younger age (median 4 vs. 23 years; $p = 0.004$).

Discussion: Compared with 2014–2021, the number of DBS samples increased 1.7-fold (320 in 3 years vs. 444 in 7 years), while diagnostic yield decreased (14.7% vs. 22.3%). The higher referral volume likely reflects increased disease awareness and expanded prenatal screening. These findings confirm that lyso-Gb1 remains a highly discriminative biomarker for GD and reflect disease severity.

Conflict of Interest: The SZMC Gaucher Unit receives support from Sanofi/Genzyme for participation in the ICGG Registry and from Takeda for the GOS Registry. A.Z. receives honoraria from Takeda, Pfizer, and BioEvents and consultancy fees from Takeda, NLC Pharma, Insightec, and Prevail therapeutics is employed by the company Agyany pharma. S.R.-V. receives grant/research support, honoraria, and advisory fee from Takeda, Pfizer, and Sanofi/Genzyme. All others- none declared.

P69- Clinical heterogeneity of the c.1880T>G (D409H) GBA1 variant: evidence from a national Gaucher disease registry

Isidro Arévalo-Vargas[1], Irene Serrano-Gonzalo[1], Sonia Roca-Esteve[1], Kohler R, Pilar Giraldo[1]

[1]Fundación para el Estudio y la Terapéutica de la Enfermedad de Gaucher (FEETEG)

Poster number: P69

Background. The c.1880T>G (p.D409H) variant in GBA1 is traditionally considered pathognomonic for Gaucher disease (GD) type 3c in the homozygous state. However, real-world data suggest that heterozygous combinations involving D409H may lead to highly variable clinical outcomes. **Methods.** We retrospectively analyzed all patients carrying the c.1880T>G variant included in the Spanish Gaucher Disease Registry (n = 24/430, 4.3%), focusing on neurological, skeletal, and survival outcomes according to genotype.

Results. As expected, all six homozygous D409H patients showed a GD type 3c phenotype. In contrast, heterozygous carriers demonstrated striking phenotypic diversity. Patients with D409H/G377S predominantly presented with adult-onset, non-neuronopathic GD type 1, whereas combinations with L444P or complex recombinant alleles were associated with severe neuronopathic disease, including epilepsy, hearing loss, psychomotor delay, and early mortality. Seven patients died within the first decade of life. Skeletal involvement was unexpectedly mild in most cases, even among splenectomized patients, although isolated severe bone disease occurred in a D409H/G377S patient following late initiation of enzyme replacement therapy. Structural skeletal deformities were observed in siblings carrying D409H/recombinant alleles. Early ERT was initiated in all pediatric cases. Adult non-

neuronopathic patients are currently well controlled on eliglustat. Adjunctive therapies (miglustat or ambroxol) failed to prevent neurological progression in neuronopathic forms.

Conclusions. The D409H variant cannot be considered a uniform predictor of GD type 3c. In heterozygous states, the associated allele critically modulates neurological severity, survival and skeletal outcomes, highlighting the need to move beyond simplified genotype – phenotype assumptions in Gaucher disease.

Conflict of Interest: None declared.

P73- The cutaneous phenotypic landscape of Gaucher disease type 1: a clinic-based cross-sectional study.

Ayelet Ollech[1,3], Chen Doga[3], Noah Sanders[3], Elena Schulman[1], Dafna Frydman[1], Tama Dinur[1], Michal Becker-Cohen[1], Ari Zimran[1,3], Shoshana Revel- Vilk[1,3]

[1]Pediatric Dermatology service, The Eisenberg R&D Authority, Shaare Zedek Medical Center, Jerusalem, Israel; [2]Gaucher Unit, The Eisenberg R&D Authority, Shaare Zedek Medical Center, Jerusalem, Israel; [3]The Faculty of Medicine, Hebrew University, Jerusalem, Israel.

Poster number: P73

Background: Cutaneous manifestations of type 1 Gaucher disease (GD1) have rarely been described, and the influence of modern treatments on skin findings is unknown.

Objective: To characterize the contemporary GD1-related skin phenotype and identify demographic, genotypic, laboratory, and drug-specific predictors.

Methods: Consecutive patients with GD1 attending the Gaucher clinic between January 2024 and May 2025 underwent a standardized dermatology examination for 20 prespecified lesions. Logistic models tested age, sex, genotype severity, laboratory tests, and current treatment.

Results: Among 101 patients (median age 31.2, range 1.5-86.1 years; 54.5 % female), 99 % exhibited ≥ 1 skin lesion. Novel findings included palmar erythema (53.5 %), rosacea (45.5 %), and atypical café au lait macules (20.8 %). Other prevalent lesions were purpura/ecchymoses (50.5 %), easy burning (48.5 %), and yellow brown skin dyschromia (38.6 %). Age independently raised the odds of angiomas, telangiectasia, purpura/ecchymoses, slow wound healing, and yellow-brown discoloration (per-year aORs ~1.02–1.04, all $p < 0.05$) and decreased the odds of pallor (aOR 0.97, 0.95–1.00, $p = 0.049$).

Male sex was associated with telangiectasia (OR 3.74, 1.38–10.14) and palmar erythema (aOR 2.39, 1.06–5.37). Any GD-1 treatment raised skin dyschromia nearly three-fold aOR 2.81 (95% CI 1.03–7.65, $p = 0.044$). Past treatment was associated with lower purpura/ecchymoses aOR 0.30 (95% CI 0.09–0.95), $p = 0.041$. Among treated patients, ERT vs SRT showed no differences for core lesions. Higher alanine aminotransferase levels were also associated with increased odds of telangiectasia (aOR 1.04 per unit, 1.00–1.08). Genotype severity was not associated with skin lesions.

Conclusions: Cutaneous involvement in GD1 is nearly universal and more prevalent than in the general population. The broadened skin spectrum we describe, including several novel lesions, provides easily recognizable clinical markers and highlights therapy-specific patterns that should guide counseling and dermatologic surveillance.

Conflict of Interest: The SZMC Gaucher Unit receives support from Sanofi/Genzyme for participation in the ICGG Registry and from Takeda for the GOS Registry. A.Z. receives honoraria from Takeda, Pfizer, and BioEvents and consultancy fees from Takeda, NLC Pharma, Insightec, and Prevail therapeutics is employed by the company Agyany pharma. S.R.-V. receives grant/research support, honoraria, and advisory fee from Takeda, Pfizer, and Sanofi/Genzyme. All others- none declared.

P74- Expanded Newborn Screening for Gaucher Disease: Insights from a Regional Network Experience

Filippo Pigani[1], Alberto Zampieri[1], Sofia del Pra[1], Giulia Gortani[2], Paolo Peruzzo[3], Emanuela Zanatta[3], Annalisa Sechi[3], Andrea Magnolato[2], Maurizio Scarpa[3], Andrea Bordugo[3], Andrea Dardis[3], Irene Bruno[2]

[1]University of Trieste, Trieste, Italy; [2]Institute for Maternal and Child Health IRCCS "Burlo Garofolo", Trieste, Italy; [3]Regional Coordinator Centre for Rare Diseases, University Hospital of Udine

Poster number: P74

Background: The inclusion of Gaucher disease type 1 (GD1) in newborn screening (NBS) programs remains controversial worldwide, as early diagnosis often precedes symptom onset by several years with no need for immediate treatment in most cases. In Italy, GD1 has been introduced in the screening panels through regional programs and pilot initiatives.

Methods and Observations: We report five pediatric cases of GD1 identified through NBS and followed longitudinally in Friuli Venezia Giulia Region. **Patient 1**, 7 years of age, low beta-glucosidase (BGLU) activity and high GlcSph at birth, at 5 years started enzyme replacement therapy (ERT) due to fatigue and slight increase in liver and spleen volumes. **Patient 2,** 6 years of age, low BGLU activity and GlcSph persistently elevated but clinically stable with normal growth, hematological parameters, and no organomegaly. She is still off treatment. **Patient 3**, 5 years of age, low BGLU activity and high GlcSph at birth developed progressive splenomegaly and increasing GlcSph during follow-up, prompting ERT initiation at 21 months. **Patient 4,** 5 months of age, low enzymatic activity and high GlcSph, normal liver and spleen size is on regular clinical and instrumental follow up. **Patient 5**, recently diagnosed, showed reduced BGLU activity, slightly increased GlcSph is currently under close monitoring. All patients presented biallelic GBA1 pathogenic variants.

Discussion: NBS for GD1 shifts the clinical focus from diagnosis to longitudinal risk stratification. Treatment decisions rely on integrated follow-up, including clinical evolution, hematological findings, growth patterns, and supportive biomarkers as GlcSph. Isolated biomarker elevation does not necessarily predict short-term clinical progression.

Conclusions: Our experience supports an individualized, surveillance-based management strategy for GD1 patients identified through NBS. Careful longitudinal monitoring allows ERT to be safely deferred in selected patients. Communication strategies and psychological burden should be taken in account.

Conflict of Interest: None declared.

P75- Current bone screening practices in patients with Gaucher disease in the US: A retrospective cohort analysis of administrative claims data, 2016-2024

Chanan Stauffer[1*], Carlos Prada[2*], Gabriela Perichon[3], Judy Hull[3], Jenny L. Carwile[3], Natalia Petruski-Ivleva[3], Siddhi Umarje[3], Kalyani Hawaldar[3],Maja Gasparic[4]

[1]Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, NY, USA; [2]Edwards Family Division of Genetics and Rare Diseases, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA Department of Pediatrics, Northwestern University Feinberg School of Medicine, Chicago, IL, USA; [3]Sanofi, Cambridge, MA, USA. [4]Sanofi, Amsterdam, Netherlands.

Poster number: P75

In Gaucher disease (GD), skeletal manifestations, including bone pain, bone crisis, osteonecrosis, and increased fracture risk, are debilitating and highly prevalent; regular bone monitoring is recommended for pediatric and adult patients with GD. To assess adherence to these recommendations, we aimed to describe bone health screening practices in patients with GD in the US. We identified a retrospective cohort of 607 patients with GD using data from a large administrative claims database (Merative MarketScan) collected between January 2016-June 2024. Patients were included if they had ≥2 claims with ICD-10 code E75.22 ≥30 days apart or ≥1 GD treatment claim; patients must have been continuously enrolled for ≥365 days after GD classification. Separately for bone screening tests (bone x-ray, dual-energy X-ray absorptiometry, and bone MRI) and biomarker tests (chitotriosidase and glucosylsphingosine), we estimated the proportion of patients with GD who received ≥1 test, the median number of tests among patients with ≥1 test, and screening rate per person per year (PPPY). Analyses were stratified by treatment status and age (data not shown). Among 455 treated patients [median (25th, 75th percentile) follow-up time= 1,069 (699.5, 1757.5) days], 57.4% received ≥1 bone screening test (median tests=2). Among 152 untreated patients [median (25th, 75th percentile) follow-up time= 969 (612.3, 1492.3) days], 39.5% received ≥1 bone screening test (median tests=2). The rate (95% confidence interval) of bone screening was 0.54 (0.50, 0.58) PPPY in treated patients and 0.29 (0.25, 0.35) PPPY in untreated patients. Biomarker testing was slightly less frequent (50.3% of treated patients and 30.3% of untreated patients with ≥1 test). Limitations include lack of data on GD type and time on therapy. This study identifies a potential gap in current bone monitoring practices in patients with GD. Increased provider awareness and adherence to screening recommendations are critical to prevent irreversible skeletal complications.

Funding: Sanofi

Acknowledgement: Editorial support for this abstract was provided by Jogindersingh Paneysar from Sanofi. This abstract is an encore version of the WORLD 2026 abstract.

Conflict of Interest: CS reports a relationship with Sanofi that includes consulting or advisory; CP has received consulting funding from Sanofi, Takeda, Orchard, and Moderna; GP, JH, JLC, NP, SU, KH, and MG are employees of Sanofi and may hold stock/stock options.

P76- The role of fat fraction quantification to determine the degrees of bone marrow infiltration in patients with type 1 Gaucher Disease. A study of the Argentinian Group for the Diagnosis and Treatment of Gaucher disease

Guillermo I. Drelichman[1], Barbara C. Soberon[1,2], Nicolás Fernández Escobar[1,2], Gabriel H. Aguilar[3], Maria S. Larroude[3], Nora Basack[2], Karina D'aloi [4], Lujan Lozano[5], Marcela Aznar[6], Mandrile Araceli [7]

[1]Consultorio de Enfermedades Lisosomales, Buenos Aires, Argentina; [2]Hospital de Niños Ricardo Gutiérrez, Buenos Aires, Argentina; [3]Centro Rossi, Buenos Aires, Argentina; [4]Hospital General de Niños Pedro Elizalde, Buenos Aires, Argentina; [5]Hospital General de agudos José María Ramos Mejía, Buenos Aires, Argentina; [6]Hospital de Niños Sor María Ludovica, La Plata, Prov. Bs. As. Argentina; [7]Hospital Paroissien, Prov. Bs As. Argentina

Poster number: P76

Introduction: BMI is a key manifestation in GD1 due to the possibility of being associated with new osteonecrosis despite being treated. Its quantification is essential for clinical follow-up and bone prognosis. Magnetic resonance imaging (MRI) using Dixon sequences is used to estimate FF, offering an objective and reproducible tool. Objective: To determine the most effective methodology to quantify BMI in adult patients(P) with GD1 treated with enzyme replacement therapy with Imiglucerase (ERT-I), integrating radiological parameters (Bone Marrow Burden (BMB) and FF), clinical parameters (therapeutic adherence) and biochemical parameters (Lyso-GL1).

Material and Methods: from 1/2018 to 1/2024, 277 bone MRI and 82 Lyso-GL1 were analyzed in 82 P >15 years old (y) with GD1 treated with ERT-I (mean (m) 12.4 y). BMI was classified using BMB and FF, quantified with Dixon sequences. The results were correlated with Lyso-GL1 levels (ng/mL) and adherence (AD) to treatment. Results: The P were grouped according to the degree of BMI into: mild/absent: (28.2%), m FF: 41% , m Lyso-GL1: 85.2 and m AD to ERT-I: 92%). Moderate: (52%), m FF 30%, m Lyso-GL1:170 and m AD to ERT-I: 72%. severe: (20%), m FF: 11.3%, m of Lyso-GL1:580 and m of AD at ERT-I: 56%. We found significant correlations between FF and BMB (r=0.71), FF and Lyso-GL1 (r=-0.65), BMB and Lyso-GL1 (r=0.68), all $p<0.001$. Lower FF was associated with higher BMI, lower AD, and higher levels of Lyso-GL1. In the group with severe BMI, 7 developed new osteonecrosis. Conclusion: Quantification by FF is a robust radiological biomarker to evaluate BMI in GD1. Its combination with BMB, Lyso-GL1 and AD to ERT-I improves bone risk stratification and therapeutic follow-up, highlighting its value in radiological practice.

Conflicts of interest: G.I.D, B.C.S, N.F.E, M.L., and G.A have received honoraria for conferences from Sanofi

---

P77- Usefulness of quantifying bone marrow infiltration as a predictor of new osteonecrosis in patients with type 1 Gaucher disease treated with enzyme replacement therapy: A study of the Argentinian Group for the Diagnosis and Treatment of Gaucher disease

Guillermo I. Drelichman[1], Barbara C. Soberon [1,2], Nicolas Fernández Escobar [1,2], Maria S. Larroude[3], Nora Basack[2], Gabriel H. Aguilar[3], Paola Reichel [4], Analia Carvani [5], Viviana Caruso[6], María Nazareth Esquivel Marín[7]

[1]Consultorio de Enfermedades Lisosomales, Buenos Aires, Argentina; [2]Hospital de Niños Ricardo Gutiérrez, Buenos Aires, Argentina; [3]Centro Rossi, Buenos Aires, Argentina; [4]CePSI "Eva Perón". Santiago del Estero. Argentina; [5]Hospital Interzonal General Agudos, Prov. Bs As. Argentina; [6]Hospital General de agudos Parmenio Piñero, Buenos Aires, Argentina; [7]Hospital Avelino Castelan, Chaco, Argentina

Poster number: P77

Material and Methods: retrospective study in 151 patients(P) ≥ 10 years(y) treated with ERT-I followed from 12/2012 to 12/2024. Age media (M) at admission: 27 y. We evaluated the P in 2 groups: Group 1: AD to ERT-I < 80%. 45 P, M AD: 61%; Group 2: AD to ERT-I ≥ 80%. 106 P, M AD 88.8%. M of ERT-I previous to study 9.2 y. M of ERT-I during the study 10.3 y. The BMI was assessed by the semi-quantitative method of the Bone Marrow Burden Score (BMBs): Normal: 0-4; moderate: 5-8; severe: 9-16. Results: 1) Bone findings prior to the study (n:151 P): BMBs: M: 8 (r: 6.00-16.0). BMI: 100%. Erlenmeyer: Yes: n:88 (58.3%). Infarcts: Yes: n: 89 (58.9%). Necrosis: Yes: n:44 (29.2%) and Fractures: Yes: N:12 (8%). 2) Bone findings at the end of the study: Group 1 vs. Group 2: BMBs: M: 12 (r: 7-16). BMI: 100% Vs. BMBs: M: 3 (r: 2-3). BMI: 0% (P=< 0.001). Erlenmeyer: Yes: n: 25 (55.6%) Vs. Yes n: 63 (59.4%) (P= 0.894). Infarcts: Yes: n: 31 (68.9%) Vs. Yes: n: 62 (58.5%) (P= 0.007). Necrosis: Yes: n: 16 (35.6%) vs. Yes: n: 31 (29.2%) (P=0.612). Fractures: Yes: n: 5 (11.1%) Vs. Yes: n: 11 (10.3%) (P= 0.827). New osteonecrosis: Group 1: n: 11 (24.4%) Vs. group 2: 0 (0%) (P= 0.025). Conclusions: At the end of the study, group 1 presented: BMI: 100% (BMBs: M:12) vs. Group 2: BMI: 0% (BMBs: M :3 (P=< 0.001) and new osteonecroses: Group 1: 11 (24.4%) Vs. group 2: 0 (0%) (P= 0.025) all statistically significant differences. BMI was the only bone lesion reversible with treatment, while osteonecrosis was irreversible. AD ≥ 80% and normalization of BMI (BMBs: 0-4) are key factors to avoid new irreversible osteonecrosis.

Conflicts of interest: G.I.D, B.C.S, N.F.E, M.L., and G.A have received honoraria for conferences from Sanofi

---

P78- Untreated 75-year-old patient with Gaucher's disease

Jemuović Zvezdana[1], Miljić Dragana[1], Pekić Đurđević Sandra[1], Doknić Mirjana[1], Stojanović Marko[1], Kurćubić Boris[1], Cekić Ivana[1], Jevtić Ivan[1], Bajić Jelena[1], Đurović Nikolić Marina[1]

[1]Clinic for Endocrinology, diabetes and diseases of metabolism, University Clinical Centre of Serbia

Poster number: P78

Gaucher's disease (GD) is the most common lysosomal storage disorder inherited in an autosomal recessive pattern.

We present a case of a 75-year-old female patient who was referred to our Clinic under suspicion of GD. She was firstly examined by haematologist because of severe anaemia and splenomegaly. MSCT of abdomen showed enlarged spleen with multiple hypodense nonhomogeneous focal lesions, compressive fractures of vertebral bodies of L1 and L5 as well as signs of colitis. Laboratory findings showed severe anaemia and thrombocytopenia with increased levels of chitotriosidase. Her past medical history revealed anaemia and thrombocytopenia in her mid-thirties but never further investigated. She had cervical cancer in her forties. Ten years ago, she was hospitalized due to severe anaemia when she received several transfusions and when splenomegaly was firstly diagnosed. She has diabetes and hypertension. On admission, she was complaining about frequent bruising. She never had bone crisis. Her physical examination showed short stature with normal BMI. She had several haematomas on the skin of arms and legs. Normal heart rate, with systolic murmur with propagation to neck and axilla. Spleen was palpated 4cm under left rib cage. MR of femurs showed oedema of right femur head with BMB score 4. DXA showed severe osteoporosis. Liver and spleen volumetry were estimated 1715ml and 2107ml respectively. Echocardiography confirmed severe aortic stenosis. Chitotriosidase

was elevated 54x ULN while Lyso-GB1 was 33x ULN. FOBT was positive and calprotectin was elevated. Cardiologist and gastroenterologist suggested further diagnostics after correcting thrombocytopenia and anaemia. Finally, genetic analysis detected mutations in heterozygous state: c.882T>G (p.(His294GIn)), c1342G>C (p.(Asp448His)), c1266A>G (p.(Asn409Ser)). CYP2D6 genotyping showed normal activity levels. After receiving confirmation of GD patient began Eliglustat therapy.

We report an elderly patient with undiagnosed GD with complications (osteoporosis, colitis and hip osteonecrosis) and several comorbidities (DM, hypertension and severe aortic stenosis).

Conflict of Interest: None declared.

P79- Consensus on Bone Disease in Gaucher Disease: Definitions, Imaging, Clinical and Laboratory Correlates, and Data Harmonization

Özlem Goker-Alpan[1], **Patrick Deegan**[2], Gabriel Aguilar[3], Pilar Giraldo[3], Kasper ter Horst[4], Derralynn Hughes[5], Ravi Kamath[1], P. Kishnani[6], Shoshana Revel-Vilk[7], Uma Ramaswami[5], Raffi Schiffmann[8], Neal Weinreb[9], Ari Zimran[7]
on behalf of the Bone Disease in Gaucher Disease Consensus Workshop Faculty

[1]Lysosomal and Rare Disorders Research and Treatment Centre, Fairfax, Virginia, USA.;[2]Lysosomal Disorders Unit, Cambridge University Hospitals, Cambridge, United Kingdom; [3]Centro Diagnostico Dr Enrique Rossi, Buenos Aires, Argentina; [4]Endocrinology and Metabolism, UMC Amsterdam, The Netherlands; [5]Lysosomal Disorders Unit, Royal Free Hospital, London, United Kingdom; [6]Medical Genetics, Duke University, Durham, NC, USA; [7]Shaare Zedek Medical Centre, Jerusalem, Israel; [8]Baylor Scott and White Research Institute, Dallas, Texas, USA; [9]Human Genetics, University of Miami, Coral Gables, Florida, USA

Poster number: P79

Background: Bone disease is a major cause of irreversible morbidity in Gaucher disease (GD), yet its assessment is hampered by heterogeneous definitions, imaging protocols, severity scoring, and registry data capture. This variability limits clinical decision-making and the utility of skeletal endpoints in research. To address these gaps, an international consensus initiative was convened to establish a unified framework for the assessment and monitoring of bone disease in GD.

Methods: An international, multidisciplinary faculty of experts in GD, radiology, and metabolic bone disease convened in February 2026 for a consensus workshop, guided by pre-circulated questionnaires and combined expert presentations with structured discussions and formal consensus voting on predefined questions regarding clinical definitions, imaging practices, severity scoring, biomarker integration, and registry design.

Results: The consensus process yielded several key outcomes. Standardized definitions for core skeletal manifestations, including refined definitions for bone crisis, fractures, and osteonecrosis, were established. In imaging, a transition from the semi-quantitative Bone Marrow Burden (BMB) score towards quantitative Dixon-based fat fraction with standardized reporting language was recommended. Two comprehensive, risk-stratified clinical algorithms were developed: a general algorithm for adults and adolescents, and a separate pediatric algorithm. These algorithms integrate clinical assessment, imaging (including selective MRI use in children), and biomarkers (notably Lyso-Gb1) to categorize patients (untreated, treated-but-unstable, stable) and guide longitudinal monitoring. The pediatric algorithm emphasizes growth-adjusted bone density assessment (whole body less head with adjustment for height Z score)). Finally, the consensus calls for the adoption of a minimum core dataset for bone disease across all GD registries to facilitate data harmonization.

Conclusion: This international consensus statement provides a unified, evidence-based framework to standardize the assessment, monitoring, and reporting of bone disease in GD. Widespread adoption of these recommendations, particularly the clinical algorithms and data harmonization proposals, is anticipated to improve the consistency of clinical care, enhance the quality and comparability of registry data, and ultimately contribute to reducing the long-term skeletal burden for patients with GD.

Conflict of interest: None declared.

P80- Clinical variability in a family with type 1 Gaucher disease: single centre experience

Jovana Kostadinovic[1], Nada Krstovski[1,2], Polina Pavicevic[1,2], Jelena Lazic[1,2], Srdja Jankovic[1], Goran Milosevic[1,2], Jelena Krcunovic[1], Jovana Svorcan[1], Predrag Rodic[1,2]

[1]University Children's Hospital, Belgrade, Serbia; [2]Faculty of Medicine, University of Belgrade, Serbia

Poster number: P80

Introduction: Gaucher disease (GD) type 1 is characterized by marked clinical heterogeneity, even among individuals sharing identical GBA genotypes. Despite advances in molecular diagnostics, genotype alone remains an unreliable predictor of disease severity or progression. In addition, GBA variants represent a major genetic risk factor for Parkinson's disease (PD), extending the clinical spectrum beyond classical GD manifestations.

Aim: To illustrate pronounced intrafamilial phenotypic variability in GD and highlight the role of lyso-Gb1 in therapeutic decision-making within a single affected family.

Materials and Methods: This retrospective single-centre study included four affected family members, three of them diagnosed with GD type 1 and one with PD. Clinical presentation, laboratory parameters, GBA genotyping, biomarker dynamics and treatment responses were analysed longitudinally.

Results: All affected individuals were compound heterozygous for GBA variants c.754T>A (p.Phe252Ile) and c.1504C>T (p.Arg502Cys). Despite identical genotypes, three siblings demonstrated striking phenotypic variability. The index patient presented at age 11 with severe thrombocytopenia (PLT <50,000/mm^3), marked splenomegaly, and lyso-Gb1 of 791 ng/mL. Enzyme replacement therapy (ERT) with taliglucerase was initiated, resulting in substantial biomarker reduction; however, persistent splenomegaly prompted therapeutic switch to another enzyme (velaglucerase alpha), after which lyso-Gb1 declined to 52 ng/mL. His older sister exhibited mild anaemia and splenomegaly without thrombocytopenia; ERT with velaglucerase was initiated only after progressive lyso-Gb1 elevation during follow-up (491 ng/mL). The youngest sibling remains untreated with isolated splenomegaly and stable lyso-Gb1 <200 ng/mL. The father developed PD in adulthood, reinforcing the established association between GBA variants and neurodegeneration.

Conclusion: This family highlights the limited predictive value of genotype alone in GD type 1 and underscores the clinical utility of lyso-Gb1 dynamics in individualized treatment decisions. The coexistence of GD and PD within the same pedigree further supports comprehensive genetic counselling and long-term multidisciplinary clinical surveillance.

Conflict of Interest: None declared.

Comorbidities in Gaucher Disease (Zodiaco Room)

P86- Biliary lithiasis in Gaucher Disease: Insights on risk factors

Lucas Ferreira Teixeira[1], Gabriela Festugato Maranhão[1], Giovanna Jost Tibolla[1], Gabriela Ponte de Mattos[2], Dévora N. Randon[3], Rodrigo T. Starosta[4,5], Mário Reis Alvares-da-Silva[1,5,6], Ida Vanessa Doederlein Schwartz[3,7,8]

[1]School of Medicine, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil; [2]School of Medicine, Pontifícia Universidade Católica do Rio Grande do Sul, Porto Alegre, Brazil; [3]Graduate Program in Genetics and Molecular Biology, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil; [4]Department of Molecular and Medical Genetics (MMG), Oregon Health & Science University, OR, United States; [5]Graduate Program in Gastroenterology and Hepatology, Federal University of Rio Grande do Sul, Porto Alegre, Brazil; [6]Department of Internal Medicine, Federal University of Rio Grande do Sul, Porto Alegre, Brazil; [7]Department of Genetics, Federal University of Rio Grande do Sul, Porto Alegre, Rio Grande do Sul, Brazil; [8]InRaras, National Institute of Science and Technology in Rare Diseases, Porto Alegre, Brazil

Poster number: P86

Background: Gaucher disease (GD) is an autosomal recessive lysosomal systemic disorder with increased prevalence of cholelithiasis and cholecystitis.

Aims: Understand the risk factors for biliary lithiasis in GD.

Methods: We conducted a prospective cohort study with 43 GD patients (>18 years), with thorough clinical assessment. Chitotriosidase activity was adjusted according to CHIT1 genotype. Data were analyzed using the Mann-Whitney test for group comparisons and log-transformed for logistic regression to assess risk factors (significance threshold: $p < 0.05$; 95% confidence interval [95CI]).

Results: Group A (30%, n = 13) included patients with cholelithiasis or cholecystitis, and group B (70%, n =30) with no evidence of gallbladder disease. Cholecystectomy was performed in 7/13 (55%) of group A. Group A had median age of 38 years (IQR=13) with 55% females (7/13), while Group B had median age of 45 years (IQR=25), with 50% female (15/30). Significant between-group differences were observed in Chitotriosidase activity: Group A: 6,115 nmol/h/mg prot (IQR=6,900) vs. Group B: 4,108 nmol/h/mg prot (IQR=6,602); ($p <0.05$). Triglyceride levels: Group A: 166 mg/dL (IQR=113) vs. Group B: 100 mg/dL (IQR=41); ($p <0.05$). Our regression model identified log-transformed triglycerides (OR=17.6, 95CI 2.1-146, $p < 0.01$) and chitotriosidase (OR=3.3, 95CI 1.2-8.5, $p < 0.05$) as independent risk factors for cholelithiasis and cholecystitis in GD. No significant differences were observed between the groups in terms of splenectomy status, serum ferritin, lyso-GB1, *GBA1* genotype, age of GD diagnosis, ERT or SRT use, time on treatment, body mass index, age, and sex, metabolic syndrome.

Conclusion: Higher Chitotriosidade and triglycerides increase risk of developing cholelithiasis and cholecystitis in GD. External validation is needed to confirm these findings.

Conflict of Interest: None declared.

P87- Insights into morbidity and mortality in Gaucher Disease: a cohort study

Lucas Ferreira Teixeira[1,2], Fabiano Poswar, Dévora[2,3] Natalia Randon[2,4,5], Ida Vanessa Doederlein Schwartz[1,2,3,4,5,6]

[1]School of Medicine, Universidade Federal do Rio Grande do Sul (UFRGS), Porto Alegre, Brazil; [2]National Institute for Rare Diseases (InRaras), Porto Alegre, Brazil; [3]Medical Genetics Service, Hospital de Clínicas de Porto Alegre (HCPA), Porto Alegre, Brazil; [4]Postgraduate Program in Genetics and Molecular Biology, UFRGS, Porto Alegre, Brazil; [5]Basic Research and Advanced Investigations in Neurosciences (BRAIN)

Laboratory, Experimental Research Center, HCPA, Porto Alegre, Brazil; [6]Department of Genetics, UFRGS, Porto Alegre, Brazil

Poster number: P87

Background: Gaucher disease (GD) is a rare lysosomal disease which is classified into three clinical phenotypes based on neurological involvement. Type 1 (GD1) is non-neuronopathic, while types 2 (GD2) and 3 (GD3) are neuronopathic. The literature on morbidity and mortality in patients with GD is scarce. Aims: To evaluate the morbidity and mortality data of a Brazilian GD cohort.

Methodology: A prospective cohort study was conducted at a GD referral center in Porto Alegre, Brazil, including patients seen at the Center from 2003 to 2023 (n = 53; GD1 = 45, GD2 = 4, GD3 = 4). Clinical data were obtained through a chart review.

Results: Patients had a median follow-up time of 15 years (range, 1 month–20 years). Comorbidities were mainly cardiovascular, endocrinological, and biliary. Nine patients (17 %) died in the period of analysis (GD1 = 4; GD2 = 4; GD3 = 1). For those with GD1, the median age at death was 65 years (range 62-67 years), and the causes of death were malignancies (n=3) and sepsis (n=1); 3 of the 4 patients who died during follow-up were on enzyme replacement therapy (ERT) for a median of 3 years. In GD2, the median age at death was 5 months, and the reasons were acute respiratory failure (n=2), sepsis of unclear etiology (n=1) and liver failure (n=1); 2/4 patients were on ERT (median duration = 5 months). The GD3 patient had Sudden Unexpected Death in Epilepsy at age 27 years and had been on treatment for 26 years.

Conclusion: Our findings suggest GD patients have multiple comorbidities, but only few of them are related to mortality in our cohort - malignancy is a concern in GD1, GD2 is uniformly fatal, even when ERT is used, and the neurological manifestations remain a continuous risk in GD3. Our analysis sheds light on the unmet needs of patients with GD, and on the urge for a multidisciplinary evaluation, even in resource-limited settings.

Conflict of Interest: None declared.

P89- Systematic Exclusion of Skeletal Artefacts in the Analysis of Bone Mineral Density Response to Gaucher Disease Treatments

Carmen Minea[1], Boliang Yu[2], Patrick Deegan[1] and the MRC Gaucherite Consortium[1]

[1]Lysosomal Disorders Unit, Cambridge University Hospitals, Cambridge, United Kingdom; [2]Nuffield Department of Surgical Sciences University of Oxford, Oxford, United Kingdom

Poster number: P89

Introduction: Dual-energy X-ray absorptiometry (DXA) is widely used to assess bone mineral density (BMD) in Gaucher disease (GD). However, skeletal complications such as osteonecrosis and fractures can confound BMD measurements. As part of an ongoing project to investigate influences on BMD in GD, this study assessed the effect of systematic exclusion of skeletal artefacts on long-term DXA data from patients with Gaucher disease and evaluated longitudinal therapeutic trends.

Methods: GAUCHERITE includes clinical, radiological and therapeutic information from patients followed at all UK national specialist centres from diagnosis to September 2019 (median follow-up 17.3 years). BMD Z-scores from lumbar spine, total hip and total radius were

extracted. Data cleaning was conducted using radiological images and reports to identify potential artefacts - following International Society for Clinical Densitometry guidelines - and exclude affected regions. Lumbar Z-scores were recalculated when at least two adjacent unaffected vertebrae were available. Z-scores obtained after strontium therapy were excluded. Cleaned DXA data were aligned to annual treatment anniversaries using linear interpolation. Pre- and post-cleaning datasets were compared using non-parametric statistics. Longitudinal trends of the median of the interpolated Z-scores were assessed using Mann–Kendall and Theil–Sen analyses

Results: Of 251 recruited patients, 222 treated patients with available DXA data were included, contributing 4,229 total Z-scores. Data cleaning led to exclusion of 286 Z-scores (6.8%). Cleaning decreased mean Z-score from −0.28 to−0.40 ($p = 0.010$). Longitudinal analyses demonstrated significant increases in spine ($\tau = 0.77$, $p < 0.001$) and total hip Z-scores ($\tau = 0.62$, $p < 0.001$) over up to 28 years of follow-up, whereas radius Z-scores showed no significant trend.

Conclusion: Systematic data cleaning meaningfully influences reported BMD in GD and improves data reliability. These methods represent a platform for ongoing analysis of Gaucher-specific treatment and other interventions on BMD.

Conflict of Interest: P.D. is a consultant to Spur Therapeutics, Sanofi-Aventis and Takeda. C.M. and B.Y. None declared

---

P90- Gaucher disease screening among patients with idiopathic avascular necrosis: a prospective cohort study

Alina Kurolap,[1,2] Daniel Misinkevich,[3,4] Daniel Levin,[5] Hagit Baris Feldman,[1,2,6] Tova Hershkovitz[2,3,4]

[1]Genetics Institute and Genomics Center, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel;[2]Gaucher Clinic and Genetics Institute, Rambam Health Care Campus, Haifa, Israel; [3]Genetics Institute, Galilee Medical Center, Nahariya, Israel; [4]Faculty of Medicine in the Galilee, Bar-Ilan University, Safed, Israel; [5]Department of Orthopedics B, Rambam Health Care Campus, Haifa, Israel; [6]Gray Faculty of Medical & Health Sciences, Tel Aviv University, Tel Aviv, Israel

Poster number: P90

Background: Gaucher disease (GD) is one of the most common lysosomal storage diseases; however, diagnosis is often delayed and challenging. GD may manifest with bone involvement, including avascular necrosis (AVN), even in the absence of other systemic signs. This study evaluated the diagnostic yield of GD by screening patients with idiopathic AVN (iAVN) as a strategy to improve early diagnosis of GD.

Methods: We conducted a prospective cohort study between 2016 and 2023 at a tertiary Genetics Institute. Fifty-three adults with MRI-confirmed iAVN of the hip underwent testing for beta-glucocerebrosidase enzyme activity via dried blood spot assay and reflex GBA sequence when enzyme activity was <2.5 nmol/h/mg. For comparison, retropective information was collected from a cohort of GD patients seen at the Gaucher Clinic at the same institute, including demographic data, GBA genotype, and GD related features particullary history of AVN. Additionally, UK Biobank (UKB) data was probed for possible association between an AVN diagnosis and GBA variants.

Results: The iAVN cohort included 53 patients (59.6% male) with a mean age of 54.8 ± 13.6 years. Four patients (7.5%) had reduced enzyme activity. Eight individuals underwent GBA sequencing; none harbored pathogenic mutations. UKB had 27 individuals with an iAVN diagnosis, but none had bi-allelic pathogenic variants in GBA. In the GD clinic cohort, 8/50 patients (16%) had a history of AVN, in only one of then AVN was the presenting symptom of GD.

Conclusions: In this study, no genetically confirmed GD cases were identified in patients with iAVN. The findings suggest limited utility of routine GD screening in this population. A more selective approach, incorporating additional clinical features and individualized risk factors, may be more appropriate to improve the detection optimize diagnostic efficiency in GD.

Conflict of Interest: The study was supported by Sanofi Genzyme

---

P91- Lower HDL cholesterol at baseline assessment correlates with bone infarction in Gaucher disease and predicts new bone infarction and worsening bone density despite enzyme replacement therapy, offering potential as a bone-disease-related biomarker

Brendan Beaton[1], Derralynn Hughes[2]

[1]NSW Health Pathology, Sydney, Australia; [2]Royal Free London NHS Foundation Trust, London, United Kingdom

Poster number: P91

Introduction: An unmet need in treating Gaucher disease (GD) relates to identifying and predicting those who develop new bone infarction (BI) and worsening bone mineral density (BMD) despite treatment. Established biomarkers can assess overall disease burden and response to treatment but are limited in prediction of those at risk of worsening bone disease.

Methods: Retrospective observational data was collected for 85 GD patients at Royal Free Hospital, London, at baseline and over a 20 year follow up period.

Results: Baseline features associated with BI in 38/85 patients were median: age: 41 years (IQR: 33-38) vs 32 years (IQR: 26-44)(p=0.027); spleen volume: 1616mls (IQR: 841-2164) vs 584mls (IQR: 455-1129)(p=0.01); liver volume: 2477mls (IQR: 1873-2681) vs 1940mls (IQR: 1497-2231)(p=0.02); and HDL cholesterol: 0.6mmol/L (IQR: 0.5-0.7) vs 0.8mmol/L (IQR: 0.7-1.0)(p=0.0004). OR for low HDL associated with baseline BI was 3.5 (95%CI: 1.14-10.75)(p=0.028). 13/85 patients experienced new BI in their first 2 years of treatment. Baseline median HDL with new BI was 0.6mmol/L (IQR: 0.5-7.0) vs no new BI 0.8mmol/L (IQR: 0.7-0.9)(p=0.02). OR for new BI was 24.4 (95%CI: 0.61-1000)(p=0.09). 18/85 patients had worsening of BMD after a median of 4.5 years of ERT with median z score at lumbar spine falling from -0.6 to -1.3, compared to 37/85 whose BMD increase from -0.9 to -0.1 (p<0.0001). Median HDL was lower at baseline at 0.5mmol/L (IQR: 0.4-0.8) compared to those whose BMD increased at 0.7mmol/L (IQR: 0.6-0.95) (p=0.012). OR for decreasing BMD on treatment for low HDL was 108.3 (95%CI: 2.21-5306) (p=0.018).

Conclusions: Lower baseline HDL predicts new BI and decreasing BMD despite treatment in GD. This has not previously been reported in the literature. Interventions to increase HDL may benefit bone disease in patients with GD and warrants further study.

Conflict of Interest: None declared.

Poster Index

Poster	Topic	Room
P1–P10	Patient Perspectives	Tergeste
P11-P61	Basic Research / Laboratory- Genetics & Biochemistry / Therapies	Giusto
P62–P91	Clinical Spectrum & Comorbidities	Zodiaco