Rare 2023

The 5th International Conference on

Rare Diseases

30 November-1 December 2023, Budapest, Hungary

Abstract Book

Bioevents
Sharing Biomed Knowledge

P-01

New treatment modalities

IMPROVING MITOCHONDRIAL MEMBRANE POTENTIAL, GLYCOLYSIS AND THE ATP IMPROVES LYSOSOMAL FUNCTION AND AUTOPHAGY AND THEREFORE PREVENTS SUBSTRATE ACCUMULATION AND NEURO-DEGENERATION

Mohamed Arif[1], Radhika Ravindran[2], Mukesh Doble[2], Gayathri V[3], Kalaivani P.[3]

[1]*R & D, Phyto Specialties Pvt. Ltd., India*
[2]*Dpt. of Biotechnology, Indian Institute of Technology Madras (IITM), India*
[3]*Center for Toxicology and Developmental Research, Sri Ramachandra Institute for Higher Education, India*

BACKGROUND: The Factors linking Neurodegenerative Diseases like Parkinson's, Alzheimer's and many Lysosomal Storage Disorders are: Mitochondrial defect, Lysosomal Dysfunction and dysregulated Autophagy resulting in Substrate accumulation and Neurodegeneration. Rotenone and Aluminum Chloride are known Neurotoxins In-vitro and In-vivo.

AIM: To establish that, by improving MMP, Pyruvate and ATP levels, the Lysosomal function, Mitophagy and Autophagy can be improved and thereby Substrate accumulation and Neurodegeneration can be prevented, using a phyto-compound that has shown to improve MMP, Pyruvate and ATP levels and could prevent neurodegeneration against rotenone toxicity in SH-Sy5y cell line study.

METHODS: Cognitive and Motor disability was induced in male Wistar rats using AlCl3 and the neuroprotective effect of the orally administered Phytocompound was evaluated through estimating levels of Oxidative, Neuronal and Inflammatory Markers in hippocampus and Cortex. Behavioral and histopathological studies were also performed.

RESULTS: All the Neuronal, Oxidative and Inflammatory markers were significantly reduced in the hippocampus and cortex of Phytocompound treated animals; Shown significant improvement in Recognition, Spatial memory and Learning. In Brain Histopathology, Amyloid plaques and NFT were significantly reduced and Glial nodules or mononuclear infiltration were totally absent.

CONCLUSION: Mitochondrial ATP is required for the V-ATPase to acidify endosomal and Lysosomal lumen. Therefore, by improving MMP, Pyruvate and ATP levels, the Lysosomal Function, Mitophagy and Autophagy could be improved and substrate accumulation and Neurodegeneration could be prevented.

As Mitochondrial defect, Lower ATP and Dysregulated Mitophagy and Autophagy are implicated in LSDs, Regulating the Mitochondrial system can be an effective therapeutic target in treating LSDs.

P-02

Relations between rare diseases and common disorders

ORAL MANIFESTATIONS OF MALES WITH PRIMARY SJOGREN'S SYNDROME (pSS) WHO ALSO HAVE KLINEFELTER'S SYNDROME (47,XXY).

Nelson Rhodus[1], Valerie Harris[2], Xavier Mariette[3], Christopher Lessard[2], John Harley[2], Kathy Sivils[2], Hal Scofield[2]

[1]*Diagnostic and Biological Sciences, University of Minnesota, MN, Saint Paul, USA*
[2]*Arthritis & Clinical Immunology Program, Oklahoma Medical Research Foundation, USA*
[3]*Center for Autoimmune Genomics and Etiology (CAGE), Cincinnati Children's Hospital, USA*

Background: Klinefelter syndrome (47,XXY) is a rare condition due to the presence of an extra X chromosome that affects sexual development in males. The signs and symptoms of 47,XXY vary. Primary Sjögren`s syndrome (pSS) is characterized by dry eyes and dry mouth is one of the most common autoimmune diseases. pSS has a robust female-to-male sex bias (20:1).

Objectives: The objective of this study was to determine the prevalence and the oral manifestations of 47,XXY among men with pSS. Methods: We evaluated 47,XXY by examination of fluorescence intensity of single nucleotide polymorphisms from the X and Y chromosomes. Subjects underwent custom genotyping platform (Immunochip, Illumina), which contained approximately 200,000 SNPs. Using Illumina Genome Studio we examined raw fluorescence data from single nucleotide polymorphisms (SNPs) for the presence of either one or two X chromosomes. We have previously confirmed using karyotype and fluorescent in situ hybridization (FISH) that this method using SNP b plot analysis correctly identifies both normal (46,XY) and Klinefelter`s (47,XXY) men. We also examined for oral conditions in these subjects.

Results: Among 136 pSS men there were 4 with 47,XXY. This was significantly different from controls (1 of 1254 had 47,XXY, p=0.0012 by Fisher`s exact test). The oral manifestations in the 47,XXY subjects included a higher prevalence of xerostomia, missing teeth, impacted teeth, taurodontism, caries, periodontal disease and candidiasis.

Conclusions: These results are consistent with the hypothesis that the number of X chromosomes is critical for the female bias of pSS and males with 47,XXY have a higher prevalence of several oral conditions.

P-03

Rare variants of rare diseases

HGSNAT GENE MUTATIONS CAUSE LYSOSOMAL STORAGE IN PODOCYTES AND AFFECTS THE STRUCTURAL INTEGRITY OF THE RENAL GLOMERULUS

Carlos R. Morales
McGill University, USA

Background: Mucopolysaccharidosis IIIC (MPSIIIC) is a RARE lysosomal storage disorder caused by a deficiency of the enzyme heparan acetyl-CoA: α-glucosaminide N-acetyltransferase (HGSNAT), which catalyzes the acetylation of heparan sulfate (HS). HS is a component of basement membranes and must be processed by HGSNAT to ensure its proper hydrolysis, thus preventing its accumulation in the lysosomes of all bodily tissues. The pathological effects of MPSIIIC are particularly noticeable in the renal corpuscles due to their abundant basement membranes.

Methods: The present study focuses on a specific missense mutation causing MPS IIIC, namely HgsNatP304L, and on a HgsNat KO mouse model generated by “Gene Tapping” to observe which cortical structures were affected. More precisely, the aim of this investigation was to identify which intraglomerular cell of the renal corpuscle displays atypical characteristics. The hypothesis being tested was that: “podocytes deficient on HGSNAT, (rather than intraglomerular mesangial cells), present lysosomal buildup, alluding to their role in maintaining the structural integrity of the renal glomerulus”.

Results and Conclusions: Light and electron microscopy of both genetically modified mice revealed an accumulation of vesicles with undigested HS in podocytes, suggesting their involvement in processing glomerular basement membranes. The parietal cells of the Bowman`s capsule, which share the same embryologic origin of the podocytes, also strayed from their wildtype morphology. Epithelial cells of the distal convoluted and collecting tubules were filled with vesicles at their apical region, whereas the proximal convoluted tubules remained unaffected, implying a difference in the mechanism of HS processing depending on the renal tubular component.

P-04

Role of registries and big data

DEVELOPMENT OF AN INTELLIGENT DATA ECOSYSTEM FOR RARE CANCERS. THE EXPERIENCE OF THE IDEA4RC PROJECT

Annalisa Trama[1], Eugenio Gaeta[2], Consortium IDEA4RC

[1]*Epidemiology and Data Science, Fondazione IRCCS Istituto Nazionale Dei Tumori, Milan, Italy*
[2]*LifeSTech, Department of Photonics and Bioengineering, Escuela Técnica Superior de Ingenieros de Telecomunicación, Universidad Politécnica de Madrid, Spain*

Background

Analysing large and diverse datasets available in electronic formats in different clinical centres would greatly advance the knowledge on rare cancers. Current hurdles include lack of interoperability and the difficulties to comply with EU data protection requirements when sharing health data.

Objectives

To develop a European data ecosystem for rare cancers, where scientific and clinical questions can be addressed by training suitable machine learning models on an ensemble of data sets contributed by several clinical centers across Europe.

Methods

Legal, ethical and privacy issues will be worked out in a way that is compliant not only with community and national regulations but also with the willingness to share of the different subjects.

Structured and unstructured data will be harmonized to extract value and knowledge.

The ecosystem will be tested in specific use cases across 11 expert centers of the European Reference Network on rare adult solid cancers.

Results

To address legal and privacy-related issues, IDEA4RC ecosystem will use a privacy preserving federated infrastructure based on secure processing environments,that will allow to train algorithms on several data sets without moving them from their original location.

IDEA4RC will develop and train Natural Language Processing models in several languages to transform notes and reports in structured data.

Data will be harmonized accordingly to the HL7 FHIR (Fast Healthcare Interoperability Resource) standard or to the Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM).

Conclusions

IDEA4RC will contribute to increase the understanding of rare cancers and will aid the clinical decision-making.

P-05

Role of registries and big data

A FRAMEWORK FOR DISCOVERING DIGITAL BIOMARKERS USING xAI AND EHR FOR RARE DISEASES

Yu-Chi Chang[1], Wei-Hsu Wang[1,2], Iau-Quen Chung[2], Tong-Ying Juang[1]

[1]*The Department of Computer Science and Information Engineering, National Taipei University, Taiwan*
[2]*The Department of New Business Development, MEDWEL Inc., Taiwan*

Background: Rare diseases often pose diagnostic challenges due to their limited prevalence and diverse manifestations. This study proposes a framework that harnesses explainable AI (xAI) and electronic health records (EHR) to discover digital biomarkers for early detection, disease progression, and therapeutic strategies for rare diseases.

Objective: Our primary goal is to develop a systematic approach that utilizes EHR data and xAI techniques to identify digital biomarkers specific to rare diseases. These biomarkers have the potential to revolutionize early diagnosis and patient care.

Methods: We selected features as potential digital biomarkers from the dataset based on the digital biomarker definition and attributes and feature selection methods. Additionally, we conducted an in-depth analysis of the methods and tools applied within the framework, such as SHAP and LIME for explainable AI models after survey papers indexed in PubMed within the last 5 years.

Results: Following our analysis, we compiled and summarized information in tables and figures. These include a figure illustrating the proposed framework, tables summarizing various methods and tools used for training interpretable and explainable AI models, and a table detailing feature selection techniques. Furthermore, we highlighted the limitations of digital biomarkers and discussed the considerations applied in the framework for rare diseases.

Conclusion: The framework presented in this study helps identify digital biomarkers for diagnosing, monitoring disease progression, and guiding therapy for rare diseases. We also provide insights into the methods and techniques for integrating EHR with xAI. To further validate the framework and discover novel digital biomarkers, we are implementing an experiment focused on the Huntington disease later.

P-06

New treatment modalities

DEVELOPMENT OF A NEW NON-INVASIVE APPROACH TO THE TREATMENT OF INFANTILE HEMANGIOMA WITH GROWTH-INHIBITING ENDOGENOUS FACTORS

Diana Dzidziguri[1], Zurab Vadachkoria[4], Giorgi Ghibradze[4], Eliza Markarashvili[2], Irina Modebadze[1], Levan Rusishvili[1], Nino Kharaishvili[3], Manana Berulava[5], Tornike Leverashvili[1]

[1]*Department of Biology; Faculty of Exact and Natural Sciences, Ivane Javakhishvili Tbilisi State University, Georgia*
[2]*Department of Chemistry; Faculty of Exact and Natural Sciences, Ivane Javakhishvili Tbilisi State University, Georgia*
[3]*Faculty of Medicine, Ivane Javakhishvili Tbilisi State University, Georgia*
[4]*Department of Children and Adolescent Maxillo-Facial Surgery and Surgical Stomatology, Tbilisi State Medical University, Georgia*
[5]*Department of Biology, Sokhumi State University, Georgia*

Background: Infantile hemangioma is a benign vascular tumor, the main reason for the development of which is genetic disorders occurring in embryogenesis. It should be noted that all methods of treating the disease, both general and local, have potential negative risks and side effects. In the cells of almost all phylogenetically distant organisms, a complex of thermostable proteins (TPC) has been identified, which has the ability to inhibit the mitotic activity of cells by inhibiting transcription. In the experimental model of hemangioma it has been established that inhibition of capillary growth can only be achieved by injection. The aim of the work was to develop a new, less invasive method of hemangioma treatment with endogenous factors.

Research object and material: adolescent white rats and chickens, blood and postoperative material of patients diagnosed with hemangioma, and liver tissues from adult rats.

Methods: TPC isolation from hemangioma cells, immobilization in polyvinyl alcohol functional polymer and in vivo activity study.

Results: TPC of chicken's liver injected into the functional polymer retains the ability to suppress the proliferative activity of the homologous tissue of adolescent rats. The mitotic activity of the liver cells of the experimental group animals was reduced by 37% compared to the corresponding indicator of the control group.

Conclusion: Chicken's liver protein complex immobilized in polyvinyl alcohol functional polymer and administered non-invasively into the skin of adolescent white rats does not have a negative impact on the histoarchitectonics of the homologous tissue and retains the ability to suppress the proliferative activity of homotypic cells.

P-07

Single gene diseases

MODELING OF FAN1 DEFICIENT KIDNEY DISEASE USING HUMAN INDUCED PLURIPOTENT STEM CELLS DERIVED KIDNEY ORGANOID SYSTEM

Dohyun Na[1,2], Sun Woo Lim[1], Hanbi Lee[1,2], Xianying Fang[1], Sheng Cui[1], Yoo Jin Shin[1], Chul Woo Yang[1,2], Byung Ha Chung[1,2]

[1]*Transplantation Research Center, The Catholic University of Korea, South Korea*
[2]*Division of Nephrology, Department of Internal Medicine, Seoul St. Mary's Hospital, South Korea*

Karyomegalic interstitial nephritis (KIN) is a genetic kidney disease caused by mutations in the FANCD2/FANCI-Asociated Nuclease 1 (FAN1) gene on 15q13.3, resulting in karyomegay and fibrosis of kidney cells though incomplete repair of DNA damage. The aim of this study was to explore the possibility of using human induced pluripotent stem cells (hiPSCs) derived kidney organoid system for modeling FAN1-deficient kidney disease, so called KIN. We generated kidney organoids using WTC-11 (wild-type) hiPSCs and FAN1-mutant hiPSCs (KIN patient derived hiPSCs and FAN1 edited hiPSC (WTC-11FAN1+/-) with CRISPR/Cas9 system in WTC-11-hiPSCs). Kidney organoids of each group were treated with 20 nM of mitomycin C (MMC) for 24 or 48 hr and expression levels of Ki67 and H2A histone family member X (H2A.X) were analyzed to detect DNA damage and cells' viability consisting of kidney organoid. WTC-11-hiPSCs and FAN1-mutant hiPSCs were successfully differentiated into kidney organoids without structural deformities. They expressed typical nephron markers. MMC treatment for 48 hours significantly increased DNA damage markers such as Ki67 and H2A.X. Viability of cells was decreased in FAN1-mutant kidney organoids. However, these findings were not found in WTC-11-kidney organoids. These results suggest that FAN1-mutant hiPSCs derived kidney organoids can recapitulate the phenotype of FAN1-deficient kidney disease. Thus, they could be used as a valuable platform to investigate the link between DNA damage and the progression of CKD in human in the future.

P-08

New treatment modalities

CRISPR/Cas9-MEDIATED SUPPRESSION OF A4GALT RESCUE ENDOTHELIAL CELL DYSFUNCTION IN A HUMAN INDUCED PLURIPOTENT STEM CELL DERIVED FABRY DISEASE VASCULOPATHY MODEL

Seung Yun Chae[2], Yoo Jin Shin[1], Hanbi Lee[1,2], Xianying Fang[1], Sheng Cui[1], Sun Woo Lim[1], Chul Woo Yang[1,2], Byung Ha Chung[1,2]

[1]*Transplantation Research Center, College of Medicine, The Catholic University of Korea, South Korea*
[2]*Division of Nephrology, Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, the Catholic University of Korea, South Korea*

Background: Fabry Disease (FD) patients display increased intima-media thickness and dilated arteries with abnormal flow patterns, leading to disrupted blood flow and a pro-thrombotic state. This dysfunction could contribute to higher cardiovascular mortality.

Objectives: We aimed to investigate the efficacy of CRISPR/Cas9-mediated A4GALT suppression in rescuing endothelial dysfunction in Fabry disease endothelial cells (FD-ECs) derived from human induced pluripotent stem cells (hiPSCs).

Methods: We differentiated hiPSCs (WT (wild-type), WTC-11), GLA-mutant hiPSCs (GLA-KO, CMC-Fb-002), and CRISPR/Cas9-mediated A4GALT-KO hiPSCs (GLA/A4GALT-KO, Fb-002-A4GALT-KO) into ECs and compared FD phenotypes, and endothelial dysfunction. We also analyzed the effect of A4GALT suppression on the reactive oxygen species (ROS) formation, and transcriptome profiles through RNA sequencing.

Results: GLA-mutant hiPSC-ECs (GLA-KO and CMC-Fb-002) showed downregulated EC markers and significantly reduced α-GalA expression, increased Gb-3 deposition, and intra-lysosomal inclusion bodies. However, CRISPR/Cas9-mediated A4GALT suppression in GLA/A4GALT-KO and Fb-002-A4GALT-KO hiPSC-ECs increased the expression of EC markers and rescued these FD phenotypes. GLA-mutant hiPSC-ECs failed in tube formation and migration into the scratched wound area. In contrast, A4GALT suppression improved tube formation and cell migration capacity. In GLA-KO hiPSC-ECs, western blot analysis revealed downregulated MAPK, and AKT phosphorylation, while SOD and catalase were upregulated. However, suppression of A4GALT restored these protein alterations. RNA sequencing analysis demonstrated significant transcriptome changes in GLA-mutant EC especially in angiogenesis, cell death and cellular response to oxidative stress, which were effectively restored in GLA/A4GALT-KO hiPSC-ECs.

Conclusions: CRISPR/Cas9-mediated A4GALT suppression rescued FD phenotype and endothelial dysfunction in GLA-mutant hiPSC-ECs, presenting a potential therapeutic approach for FD-vasculopathy.

P-09

General challenges in rare disease

STEP BY STEP MANAGEMENT OF CONGENITAL CHYLOUS ASCITES IN A NEONATE

Fereshteh Karbasian[1], Zahra Vahedi[2], Farhad Abolhassan Choobdar[2]

[1]*Pediatric Gastroenterology, Iran University of Medical sciences, Iran*
[2]*Neonatology, Iran University of Medical sciences, Iran*

Congenital chylous ascites is a rare condition that occurs when lymphatic fluid (chyle) accumulates in the abdominal cavity due to a malformation or blockage in the lymphatic system. It is present at birth and can cause abdominal swelling, discomfort, and difficulty breathing. The condition is usually diagnosed in infancy or early childhood and can be managed with dietary changes, medications, and sometimes surgery.

Case presentation: a A 36-year-old female underwent an emergency C-section at 39 weeks after failed induction. A female neonate was delivered (birthweight: 3.72 kg, length: 52 cm). There was evidence of congenital ascites during pregnancy, in prenatal sonographic exams. The newborn examination confirmed the prenatal diagnosis and the baby was transferred to NICU. Parasynthesis of abdominal fluid was milky with a high triglyceride and chylous ascites was considered. As the patient did not respond to MCT oil rich formula and octreotide, it was decided on a trial of 7 day NPO for her, but after starting feeding again, ascites volume increased and an exploratory laparotomy was planned to find the lymphatic leakage site. After three days in spite of feeding the patient with hypoallergenic formula it seemed that ascites decreased and laparotomy was canceled. Afterwards she was discharged in 5 days without any ascites.

Conclusion & Significance: While managing a neonate with chylous ascites, be patient in using medical treatment to achieve the best result.

P-10

Rare variants of rare diseases

A CASE OF EPSTEIN-BARR VIRUS ASSOCIATED HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS DURING THE COVID-19 PANDEMIC

Adith Bondugula, Shubham Garg, Basavaprabhu Achappa

Department of General Medicine, Kasturba Medical College, Mangalore, Manipal Academy of Higher Education, India

Background

The COVID-19 pandemic caused countless active infections and deaths due to hypercoagulability, hypercytokinemia, lung injuries, and secondary infections such as EBV. Epstein-Barr Virus (EBV) is a virus that generally only causes an asymptomatic infection or a mild febrile illness. However, in patients with compromised immunity a condition known as hemophagocytic lymphohistiocytosis (HLH) can manifest. In a case seen at a hospital in Mangalore, a 32 year old with no comorbidities presented with a 2 month history of recurrent episodes of fever and weight loss. He had a mild seropositive COVID-19 infection 3 months prior and was treated elsewhere. On examination, he had generalized lymphadenopathy and splenomegaly. He was then extensively evaluated.

Objectives

To determine if the patient has EBV and HLH
To determine if COVID-19 has made patients susceptible to EBV, and whether it made them more susceptible to develop HLH

Methods

Blood investigations: showed pancytopenia

Bone Marrow Aspiration Cytology: showed hemophagocytic changes

EBV DNA PCR: Positive

Results

Due to his lab results, he was diagnosed with EBV associated with HLH, and was started on Rituximab 600 mg/week, along with prednisolone. He responded very well, and 8 months post therapy he is healthy and off all medications.

Conclusion

The patient presented with a history of COVID-19 and came with complaints of pyrexia with unknown origin. On laboratory investigations he was found to have EBV and HLH. Upon starting treatment with rituximab and prednisolone he recovered and achieved remission.

P-11

Miscellaneous rare diseases

KNOWN VARIANTS IN HEREDITARY ERYTHROCYTOSIS ALSO IDENTIFIED IN SPORADIC "IDIOPATHIC" PATIENTS

Andrea Benetti, Irene Bertozzi, Maria Luigia Randi

First Medical Clinic, Department of Medicine – DIMED, University of Padova, Italy

Background:

Absolute erythrocytosis is a clinical condition characterised by an increased red cells production, resulting in haemoglobin and haematocrit levels above the reference range. There are rare congenital hereditary erythrocytosis forms classified as primary when erythropoietin receptor gene (*EPOR*) is altered and secondary when genes involved in the oxygen sensing pathway (OSP) or in globin's genes are altered. When no cause is identified, we talk about Idiopathic Erythrocytosis (IE).

Objective:

To search an explanation for sporadic IE patients.

Methods:

An ad hoc Next Generation Sequencing (NGS) panel comprehending genes known to cause erythrocytosis (*EGLN1*, *EPAS1*, *VHL* and *EPOR*) was used to search germline variants in 118 sporadic patients (M/F =101/17; mean age 53.7±17.2 years) with an unexplained, not familial erythrocytosis.

Results:

We found *EGLN1* variants in 18 patients (15%), *EPAS1* in 6 (5%), *VHL* in 3 (2.5%) and *EPOR* in 8 (6.7%) (detailed variants in *Table 1*).

Conclusions:

Some of the alterations we found, such as *EGLN1*Cys127Ser (Tibetan variant), have been repeatedly observed in familial erythrocytosis, while some of other alterations have never been described before. The latter need to be evaluated to ascertain their relevance in erythroid iron metabolism. Our data show that in not-familial IE patients, variants in genes of OSP and *EPOR* may be found, suggesting that erythrocytosis may be, at least in some cases, due to these alterations. Our observation must be confirmed with other studies, but it suggests to evaluate these genes not only in familial erythrocytosis but also in sporadic cases of IE.

Table 1: Variants of our sporadic IE patients

Gene / Chr	Coding Region Change	Protein Change	Exon	rs code	Patients for variant	N. of patients
EGLN1 (PHD2) Chr1	c.380C>G	p.Cys127Ser / C127S	1	rs12097901	11	18
	c.471C>G	p.Gln157His / Q157H	1	rs61750991	6	
	c.806T>C	p.Ile269Thr / I269T	3	/	1	
	c.1108C>G	p.Arg370Gly / R370G	1	rs54154228	1	
EPAS1 (HIF-2α) Chr2	c.1121T>A	p.Phe374Tyr / F374Y	9	rs150797491	4	6
	c.2296A>C	p.Thr766Pro / T766P	15	rs59901247	1	
	c.1648C>T	p.Arg550Trp / R550W	12	rs771840848	1	
VHL Chr3	c.74C>T	p.Pro25Leu / P25L	1	rs35460768	3	3
EPOR Chr19	c.296C>T	p.Ala99Val / A99V	3	rs146235694	1	8
	c.1194T>G	p.Asp398Glu / D398E	8	/	1	
	c.543G>C	p.Glu181Asp / E181D	4	/	1	
	c.1460A>G	p.Asn487Ser / N487S	8	rs62638745	4	
	c.137G>A	p.Gly46Glu / G46E	2	rs45516306	1	

P-12

Rare syndromes

SCREENING OF VISUAL PATHWAY IN PATIENTS SUFFERING FROM GUILLAIN-BARRE BY VISUAL EVOKED POTENTIAL

Fatemeh Sarzaeim[1], Seyed Mohammad Masoud Shushtarian[2], Ahmad Shojaei[3]

[1]*Department of Neurology, Faculty of Medicine Sciences, Islamic Azad University, Tehran, Iran.*
[2]*Department of Biophysics and Biochemistry, Faculty of Advance Science and Technology, Tehran Medical Sciences, Islamic Azad University, Tehran, Iran.*
[3]*Department of Ophthalmology, Basir Eye Health Research Center, Iran University of Medical Sciences, Tehran, Iran.*

Aim:

Guillain-Barre syndrome (GBS) is a rare condition in which a person's immune system attacks the peripheral nerve. The visual system can be affected in GBS patients. The visual pathway may also undergo pathological changes in these patients using visual evoked potential (VEP).

Method:

10 patients diagnosed with GBS in the age range of 25 to 56 years were selected for the purpose of the present study.

Visual evoked potential using pattern type of stimulation was tested in the patient group using Mangoni machine. The result obtained was compared with 10 normal populations following VEP tests. SPSS version 22 was used for this purpose.

Results:

In the case and control groups were no significant differences in demographical findings as a significant difference in latency and amplitude of VEP, P100 peak was observed in the two groups.

Conclusion:

Guillain-Barre syndrome can damage the visual pathway of patients which can be measured by latency and amplified VEP, P100 peak.

Keywords:

Guillain-Barre syndrome, visual pathway, visual evoked potential

P-13

Miscellaneous rare diseases

INTEGRATING IN SILICO MOLECULAR EVOLUTION, SYNTHETIC BIOLOGY AND GENE THERAPY APPROACHES FOR THE DEVELOPMENT OF A NOVEL ENZYME FOR REPLACEMENT THERAPY FOR GAUCHER DISEASE

Lilian Figueiredo[1], Daniela Tirapelli[2], Lucas de Souza[3], Maristela Orellana[3], Dimas Covas[3], Kuruvilla Abraham[4], Flavio Lichtenstein[5], Giuliano Bonfá[6], Velia Siciliano[6], Ron Weiss[7], Stanton Gerson[8], **Aparecida Maria Fontes**[1]

[1]*Genetics, Ribeirão Preto Medical School – University of São Paulo, Brazil*
[2]*Surgery and Anatomy, Ribeirão Preto Medical School – University of São Paulo, Brazil*
[3]*Center for Cell-Based Therapy, Blood Bank of Ribeirão Preto, University of São Paulo, Brazil*
[4]*Computer Science, Institute of Mathematical Sciences and Computation, São Carlos - University of Sao Paulo, Brazil*
[5]*Center of Excellence in New Target Discovery, Butantan Institute, São Paulo, Brazil*
[6]*Center for Advanced Biomaterials for Healthcare, Istituto Italiano di Tecnologia, Napoli, Italy, Italy*
[7]*Department of Biological Engineering, Synthetic Biology Center, Massachusetts Institute of Technology, Cambridge, USA*
[8]*National Center for Regenerative Medicine, School of Medicine, Case Western Reserve University, Cleveland, USA*

Background: Gaucher Disease (GD) is a rare autosomal recessive lysosomal storage disease caused by mutations in the GBA1 gene, leading to reduced lysosomal enzyme b-glucocerebrosidase (GCase) activity. Enzyme replacement therapy is the standard treatment.

Objectives: our study investigates the use of in silico molecular evolution, synthetic biology and gene therapy approaches in developing a new recombinant enzyme.

Methods: we generated GBA variants (GBA-7, GBA-8, GBA-9, and GBA-12) from primate and non-primate genomes, along with the wild-type GBA (GBA-Opt) from Homo sapiens. Secondary and tertiary mRNA structures were determined using ViennaRNA and 3dRNA. We investigated transcriptional regulation with CMV and hEF1A promoters, alongside a GFP control construct, in 293-FT human cells.

Results: out of 208 cell lines, 137 expressed GBA, 40 expressed GBA + GFP, 8 expressed GFP, and 23 were control cells. GBA transcripts under hEF1A showed higher expression than CMV (p 0.05), with GBA-7 exhibiting 5.2-fold higher levels than GBA-Opt (p 0.05). GBA-7 also displayed the highest stability (-844 + 4.86 kcal/mol) compared to others. Co-transfecting GFP and GBA enabled more accurate assessment of enzyme properties. GCase activity was assessed in cell supernatants and lysates. Cells with GBA-7 under hEF1A promoter produced 272.5 (+38.16) nmol hydrolyzed substrate/mL/h and 507.6 (+38.16) nmol hydrolyzed substrate/mg protein/h. AlphaFold2 revealed structural alignment of GCase-7 with human GCase (UniProt P04062). In conclusion, we successfully selected GBA-7 using in silico evolution, synthetic biology, and gene therapy for potential GD replacement therapy. Further studies are needed to assess GCase-7 functionality in animal models.

P-14

Raising awareness for rare diseases

BRAIN CORTICAL COMPLEXITY AND NEUROPSYCHOLOGICAL DEFICITS IN GAUCHER DISEASE PATIENTS: THE FOLLOW-UP OF SENOPRO_GAUCHER STUDY

Gianmarco Tessari[1], Maria Giulia Tullo[2], Enza Morgillo[3], Giovanna Palumbo[4], Simona Bianchi[4], Giulia Ferrazzi[4], Alessandro von Gal[1], Cecilia Guariglia[1], Fiorina Giona[4]

[1]*PhD program in Behavioral Neuroscience, Department of Psychology, Sapienza University of Rome, Italy*
[2]*Brain Imaging Laboratory, Department of Psychology, Sapienza University of Rome, Italy*
[3]*Master Degree in Cognitive Neuroscience and Psychological Rehabilitation, Department of Psychology, Sapienza University of Rome, Italy*
[4]*Department of Translational and Precision Medicine, Sapienza University of Rome, Italy*

The present study (SENOPRO_Gaucher) lies within the broader field of research on Gaucher disease (GD), investigating type 1 and type 3 patients through the association between cerebral cortical thickness and neuropsychological performance in patients with GD.
In this study, 10 GD1 (mean age = 40.09 years, SD = 11.57 years) and 1 GD3 (age = 26) underwent a 3T MRI session including T1 scans. Afterward, a neuropsychological evaluation was performed in GD patients using a cognitive battery to assess neuropsychological deficits.
After 3 years, a follow-up including 3T MRI and neuropsychological evaluation, was performed.
Both GD1 and GD3 patients showed cognitive deterioration in verbal memory performance (15 Rey words and Babcock test). By using Freesurfer we extracted the cortical thickness (CT) in bilateral regions involved in memory.
The analysis revealed interesting correlations between verbal memory deficit and increased CT in right subparietal sulcus and left anterior transverse collateral sulcus.
We discuss three possible explanations: the first refers to the “accumulation hypothesis”. Gaucher disease is the most common sphingolipidoses with an accumulation of fibrillated aggregates (Gaucher cells). Although the main sites of accumulation are the liver, spleen and bone marrow, cerebral accumulation may increase cortical thickness. According to the literature, similar evidence was observed in visual cortex and occipitotemporal areas in GD patients.
The second hypothesis refers to outcomes caused by prolonged treatment. The outcomes caused by three years (or more) prolonged Enzyme Replacement Therapy (ERT) result in increased cortical thickness. It could be associated with the consequences of the prescribed drug treatment.
The last hypothesis is the “failed neuroplasticity”. An (ineffective) neural modification (neuroplasticity) occurs to compensate the mild cognitive difficulties following pathological processes. It results in increased cortical thickness in parietal and occipital-temporal areas.
In conclusion, the novel findings on cortical thickness and cognition here presented shade light on the specific neuropsychological correlates and cortical development of Gaucher and will contribute to a better understanding and treatment planning on such rare disease.

P-15

Rare variants of rare diseases

KIDNEY PATHOLOGY FINDINGS IN PAROXYSMAL NOCTURNAL HEMOGLOBINURA – CASE REPORT

Elena Zakharova[1], Tatyana Makarova[1], Tatyana Jylinskaya[2], Ekaterina Stolyarevich[2]

[1]*Nephrology, Botkin Hospital, Russia*
[2]*Pathology, Clinical Hospital № 52, Russia*

Background: chronic kidney disease is reported in 65% of patients with paroxysmal nocturnal hemoglobinuria (PNH). Main mechanisms of kidney damage include direct toxicity of free hemoglobin in the tubular cells; tubular obstruction by uric acid crystals and hemoglobin urinary casts-cylinders; hemosiderosis and tubular damage due to the chronic hemolysis and hemoglobinuria; and ischemic cortical necrosis due to recurrent microvascular thrombosis.

Objectives: To report a case of PNH, diagnosed based on kidney biopsy findings and confirmed by PNH clone detection.

Methods: 32-years old Caucasian male presented 14 years prior to admission with pancytopenia, diagnosed with aplastic anemia and treated with cyclosporine and autologous stem cell transplantation. Three years before admission he developed an episode of “dark” urine, which subsequently recurred every year. At admission, he complained on loin pain and “dark” urine; his total blood count was within normal range, urinalysis showed proteinuria and microhematuria, his serum creatinine was 129 μmol/L and lactate dehydrogenase was 1448 U/L. Kidney biopsy showed hemosiderin deposits in the tubular cells and focal segmental glomerulosclerosis; immunofluorescence was totally negative. Peripheral blood cells flow cytometric immunophenotyping found PNH clone in erythrocytes, granulocytes and monocytes.

Results: The patient was diagnosed with paroxysmal nocturnal hemoglobinuria; he refused eculizumab treatment and was followed during the next 8 years. His is doing well and his erythrocyte PNH clone gradually decreased from 14.1% to 9.3%

Conclusion: Paroxysmal nocturnal hemoglobinuria can be underdiagnosed, mimicking other clinical conditions, and repeated episodes of hemolysis may cause tubular hemosyderosis and lead to chronic kidney disease.

P-16

Single gene diseases

DIGIT DEFECTS IN PATIENTS WITH HOXD13 MISSENSE MUTATIONS ARE ASSOCIATED WITH THE DISRUPTION OF HOXD13 PIONEERING ACTIVITY

Marie Kmita, Rodrigue Peraldi, Rachael Paul

Genetics and Development, Institut De Recherches Cliniques De Montréal, Canada

Embryonic development relies on series of cell fate determination events, the impairment of which leads to congenital malformations. The HOX family of transcription factors (TFs) play a key role in the establishment of distinct cell fates in the developing embryo and mutations of Hox genes are responsible for numerous congenital diseases. Although Hox genes were discovered 40 years ago and were extensively studied, the understanding of the mechanisms underlying HOX-dependent cell fate specification and patterning events is still fragmentary. Recently, HOX TFs were shown to act as pioneer factors, i.e. TFs having the ability to trigger the switch from ‘closed’ to ‘open’ chromatin state leading to the accessibility of these newly opened loci to other TFs and the transcriptional machinery. Several missense mutations in HOXD13 homeodomain have been associated with digit defects in patients. Here, we present a series of analyses revealing that these missense mutations affects HOXD13 pioneering activity by preventing its interaction with the SWI/SNF chromatin remodeling complex. Our study not only provide a molecular characterization of the diseases but also helps understanding the mechanisms by which the HOX factors instruct cell fate.

P-17

Ethical aspects in rare diseases

ETHICAL ASPECTS OF RARE DISEASES: BASIC PILLARS OF ETHICS IN DIFFERENT ECONOMIES

Ferdous Ara Islam

[1]*Neurosurgery, National Institute of Neurosciences (NINS), Bangladesh*
[2]*Rare Diseases, Istanbul university (Institute of Health Science), Turkiye*

Background: Globally, 400 million (80% genetic origin) people suffer from 10.000 rare diseases and only 5% have got orphan drug treatment. Rare diseases endorse two basic pillars of medical ethics: justice and beneficence. Justice refers equitable health care whereas, beneficence refers goodwill.

Objective: This study predicts how basic pillars of ethics acts in different economies.

Methods: Relevant recent data, literature were used from Pubmed, Global Genes, EURODIS etc.

Results: Legislation of resource allocation for overall management of rare diseases is utmost important issue. Patients become marginalized without support even in developed economy. Justice, rights based approach, non abandonment; rule of rescue comes under concern. Egalitarian society brings equitable health care. Utilitarian society maximizes benefits (life expectancy, QOL, DALYs and QALYs, economic evaluation) and prioritizes. Funding for orphan drugs development, questions arise on production cost, failure, revenue generation in drug industry. Cost effectiveness depends on purchasing power of population (PPP); varies developed to developing economies. Pharmacogenetics brings issues of drug efficacy and safety for planning of Clinical trial cohort may cause genetic discrimination. Personalized medicine will be growing concern. Beneficence require sponsor for research. Rare disease pathology research also brings question of ethical issues of genetic testing (exome and whole genome sequencing). Questions also arise on neonatal and prenatal screening, availability of reference labs, genetic testing labs in developing economy.

Conclusion: Developed economies established their own policies like EU charter rights based approach (section 35, 2000/C 364/01) ensures health care. Rest of the world also needs some attention.

P-18

Role of registries and big data

UTILIZING ARTIFICIAL INTELLIGENCE / MACHINE LEARNING IN RARE DISEASES: LIVING WITH ARACHNOIDITIS - AN INTERNATIONAL STUDY BY THE ARACHNOIDITIS & CHRONIC MENINGITIS COLLABORATIVE RESEARCH NETWORK (ACMCRN)

Lori Verton, Patricia Gomes

Research, Arachnoiditis & Chronic Meningitis Collaborative Research Network, Canada

BACKGROUND: Arachnoiditis is a rare and painful disorder caused by inflammation of the spinal cord arachnoid membrane. AI and cloud computing can aid in research and treatment by enabling data analysis, pattern identification, and global collaboration. The ACMCRN Stuff That Works (STW) Survey used AI and cloud computing to conduct the largest patient-reported survey on Arachnoiditis.

OBJECTIVES: The study aimed to assess treatment effectiveness, provide a platform for patient experiences, and improve understanding of the condition. By leveraging technology and patient participation, the study sought to enhance patient care, treatment outcomes, and overall knowledge of Arachnoiditis.

METHODS: From 2021-2022, ACMCRN implemented a series of health-related surveys within their international community, conducted through the Stuffthatworks.health Platform and disseminated via a combination of targeted social media campaigns and word-of-mouth strategies, with 1250 respondents.

RESULTS: 78% indicated symptom onset in adulthood. Among a wide variety of symptoms, back and leg pain, (including difficulty sitting) and numbness were most frequently reported. Participants listed aggravating factors, comorbid conditions, and ranked 34 popular arachnoiditis treatments as either tried, effective, or detrimental.

CONCLUSION: This early attempt at employing an AI and machine-learning software platform appears to indicate that the traditional burdens of recruitment in Rare Disease may be overcome with the use of virtual software. Combined with the recruitment potential via disease advocacy/support groups, it exceeds past traditional attempts at recruiting a sizeable cohort.

These findings will be expanded upon through the ACMCRN International Arachnoiditis Patient Registry in upcoming studies. Please see more registry information at www.acmcrn.org.

(most common)

P-19

General challenges in rare disease

HOW CAN WE MODEL MUTATIONS IN ANCIENT CONSERVED HUMAN DISEASE GENES? A CASE STUDY IN C. ELEGANS

Krisztina Takacs-Vellai, Zsolt Farkas, Fanni Ősz

Dept. of Biological Anthropology, Eötvös Lorand University, Hungary

Background: The conserved B-subunit of succinate dehydrogenase (SDH) participates in the TCA cycle and mitochondrial electron transport. The Arg230His mutation in SDHB causes heritable pheochromocytoma/paraganglioma (PPGL).

Objectives: Simple animal models can be useful in the study of rare diseases thus we generated an in vivo PPGL model (SDHB-1 Arg244His; equivalent to human Arg230His) in the nematode C. elegans.
Methods: LC-MS, Seahorse and RNAseq were used to characterize the metabolism of sdhb-1(Arg244His) and sdhb-1(-) mutants. The number of functional mitochondria was determined by Mitotracker. ROS levels were measured by CellRoxGreen, expression of HIF-1 targets was determined by semi-quantitative RT-PCR.

Results: Arg244His mutants manifest delayed development, attenuated ATP production and reduced mitochondrial number. Although succinate is elevated in both missense and null sdhb-1 mutants, transcriptomic comparison suggests that only Arg244His worms elevate lactate/pyruvate levels, pointing to ‘Warburg’-like aberrant glycolysis. Accordingly, in Arg244His mutants increased expression of lactate dehydrogenase (ldh-1) was observed, which could be inhibited by LDHA inhibitors and caused arrested development. Besides ldh-1/LDHA, elevated expression of other hypoxia target genes such as pvf-1/VEGFA and Y48G10A.3/NDGR1 were detected in point mutants. In addition, Arg244His mutants displayed elevated ROS levels.

Conclusion: Characterization of our novel nematode PPGL model revealed rewired metabolism, hypoxia activation and increased ROS levels, characteristics of PPGL tumors, which can be observed in patients. We showed that our model is druggable and can be used after optimalization for high-throughput screening of drug candidates.

We thank Dr. Anil Mehta, Dr. Gordon Stewart, and the Phaeo Para Cancer Charity for their support.

P-20

Raising awareness for rare diseases

GENOTYPE-PHENOTYPE ANALYSIS OF JUVENILE NEURON CEROID LIPOFUSCINOSIS AND ISOLATED CONE-ROD DYSTROPHY ASSOCIATED NOVEL CLN3 VARIANTS

Bo Lei, Qingge Guo

Henan Eye Hospital, Henan Provincial People's Hospital, China

Background: CLN3 associated diseases show strong genetic and clinical heterogeneity.

Objectives: To determine the causative variants in CLN3 gene in two families with juvenile neuron ceroid lipofuscinosis (JNCL) complicated with heart malfunction and isolated cone-rod dystrophy (CORD), and to analysis the genotype-phenotype correlation.

Methods: Examinations including fundus photography, sweep source optical coherence tomography, visual field, and ERG were performed in individuals from two families diagnosed with JNCL and isolated CORD. WES, bioinformatics, Sanger sequencing and co-separation were performed. The pathogenicity was carried out follow the ACMG guidelines. Protein structure was predicted.

Results: All patients showed vision loss in both eyes. OCT revealed thinning, atrophic, and disorganized retina. Patients in the family F1 showed epilepsy and abnormal cardiac function, while patient in family F2 presented only retinal malfunction. We detected two compound heterozygous variants of CLN3 in the two families, including a missense variant c.982GC (p.Ala328Pro), a splicing variant c.963-13AG and two nonsense variant c.104GA (p.Trp35X) and c.263CG (p.Ser88X). c.963-13AG, c.104GA (p.Trp35X) and c.263CG (p.Ser88X) were novel variants. We also detected a novel nonsense variant c.2526CG (p.Tyr842X) in MYBPC3 in family F1. The five variants were co-segregated in the two families. Three CLN3 protein residues (Trp35, Ser88, Ala328) were highly conserved. Four variants were likely pathogenic, and one was uncertain (c.963-13AG, CLN3). Protein structure was modified by the variants.

Conclusion: Four compound heterozygous variants in CLN3 and a heterozygous MYBPC3 variant were identified in a JNCL with heart malfunction and an isolated CORD family.

P-21

Raising awareness for rare diseases

ASSOCIATION BETWEEN CENTRAL VISION AND PANRETINAL RETINAL FUNCTION IN INHERITED RETINAL DYSTROPHY PATIENTS

Qingge Guo, Shuai Ming, Ya Li, Changgeng Liu, Bo Lei

Henan Eye Hospital, Henan Provincial People's Hospital, China

Purpose: To analyze the association between central vision and panretinal photosensitivity measured by full-field stimulus threshold (FST) in inherited retinal dystrophy (IRD) patients.

Methods: This retrospective study included thirty-nine IRD patients. All the participants underwent ophthalmology examinations, including the best corrected visual acuity (BCVA) in logMAR, swept-source optical coherence tomography (SS-OCT), electroretinogram (ERG). In addition, FST was conducted with red, blue and white light stimuli. The subjects were divided into mild (≤-35dB), moderate (-35dB~-25dB) and severe (25dB) groups according to the FST results. Analysis of variance (ANOVA) was used to evaluate the differences in age and BCVA among the groups. Subjects were further divided into two groups including rod-cone dystrophy (ROCD) and cone-rod dystrophy (CORD). The difference of FST between the two groups was analyzed by Mann-Whitney Test.

Results: Only with red light stimulation, the mean age of the mild, moderate and severe groups had significantly difference (18.8±10.8, 30.2±11.9, and 34.1±11.6. P0.01). With blue and white light stimuli, BCVA presented significantly difference between the groups (Blue: P0.01; White: P0.05). Compared to ROCD patients, CORD exhibited better FST especially with blue and white stimuli (Red: P0.05; Blue: P0.01; White: P0.01), but worse BCVA (P0.05).

Conclusions: In IRD, decrease of red light driven panretinal photosensitivity with ageing could imply progressively loss of cone function. Furthermore, the results that CORD patients showed better FST but worse BCVA than ROCD were in agreement with the fact that peripheral photoreceptors were better preserved. FST may be an additional function measurement for IRD patients.

P-22

New treatment modalities

DEMOCRATIC METHOD FOR PROCESSING RARE DISEASE OMICS DATA WITH APPLICATION TO OSTEOGENESIS IMPERFECTA

Daniela Gerovska[1], Arantza Infante[2], Blanca Gener[2,3], Itziar Astigarraga[4], Clara I Rodríguez[2], Marcos J. Araúzo-Bravo[1,5,6]

[1]*Computational Biology and Systems Biomedicine, Biogipuzkoa Health Research Institute, Spain*
[2]*Stem Cells and Cell Therapy, Biobizkaia Health Research Institute, Spain*
[3]*Department of Genetics, Cruces University Hospital, Spain*
[4]*Department of Pediatrics, Cruces University Hospital, Spain*
[5]*Basque Foundation for Science, IKERBASQUE, Spain*
[6]*Cell Biology and Histology, University of Basque Country (UPV/EHU), Spain*

Osteogenesis imperfecta (OI), estimated incidence of 1 in 10,000-20,000, is a rare connective tissue disorder affecting mainly the bones, which are extremely fragile due to low bone mass. The majority of cases are caused by dominant mutations in the COL1A1 or COL1A2 genes encoding type I collagen. Mesenchymal stem cells (MSCs), as the progenitors of the osteoblasts, the main type I collagen secreting cell type in the bone, have been tested as an innovative therapy for OI with promising but transient outcomes. Reiterative infusions of histocompatible MSCs, administered over a 2.5-year period, in two OI pediatric patients overcame the short-term effect and improved the bone parameters without adverse effects. The effect of post-cell therapy sera on directing osteogenic fate of MSCs was studied by analyzing 10 different OI MSCs lines obtained from pediatric patient bone donations and discarded material, cultured in the presence of sera from one of the 2 OI patients, collected before, during, and after the cell therapy. We designed a democratic method to identify differentially expressed genes (DEGs) between the two conditions: after versus before the cell therapy. We searched for upregulated genes after treatment by giving each gene a “for”-vote in case of upregulation of more than a threshold in log2-scale in the after-treatment condition compared to the before-treatment condition, and an “against”-vote in case of downregulation over the threshold, with similar approach defining downregulation. Finally, we chose all the genes with a threshold of votes or more “for”-votes for both up- and downregulation. We used the P-value produced by a tailed paired t-test to rank the selected genes. The democratic method is suitable for any type of rare disease omics data.

P-23

New treatment modalities

EFFICACY OF MECASIN FOR TREATMENT OF AMYOTROPHIC LATERAL SCLEROSIS: A PHASE IIA MULTICENTER RANDOMIZED DOUBLE-BLINDED PLACEBO-CONTROLLED TRIAL

Sungchul Kim, Dongwoon Han, Jinyoon Lee, Joonyoung Shin

Institute for Global Rare Disease Network, Professional Graduate School of Korean Medicine, Wonkwang University, South Korea

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease causing progressive voluntary muscle paralysis. Mecasin, derived from modified jakyakgamchobuja-tang, an herbal blend containing various components, demonstrates neuroprotective and anti-neuroinflammatory effects, offering relief to ALS patients.

This trial aimed to evaluate the efficacy and safety of mecasin in these patients.

Patients were randomized to receive daily doses of mecasin at 1.6 g, mecasin at 2.4 g, or a placebo for 12 weeks. Primary assessment: Korean version of ALS Functional Rating Scale-Revised (K-ALSFRS-R) scores. Secondary measures included muscular atrophy, pulmonary function, creatine kinase levels, body weight, various scales for pain, depression, fatigue.

Among the 30 patients randomized, 24 completed the follow-up. Significant between-group differences were detected in the primary endpoint using the omnibus F-test. The changes in the K-ALSFRS-R score between 12 weeks and baseline were − 0·25, − 1·32, and − 2·78 in the mecasin 1.6 g, mecasin 2.4 g, and placebo groups, respectively. The difference in the K-ALSFRS-R score between the mecasin 1.6 g and placebo groups was 2·53 points (95% confidence interval [CI]: 0·61–4·45), and that between the 2.4 g and placebo groups was 1·46 points (95% CI: 0·48–3·40). However, no significant differences were detected in the secondary endpoints (MRC: dyspnea, p = 0·139; VAS pain,p = 0·916; forced vital capacity,p = 0·373). The incidence of adverse events was similar and low in all groups.

Mecasin may retard symptomatic progression without major adverse effects. A phase IIb study to evaluate its long-term effects in ALS is ongoing.

P-24

Single gene diseases

EXPANDING PHENOTYPE OF APDS2 WITH HYPER IgM PHENOTYPE WITH DYSMORPHISM AND INCOMPLETE PENETRANCE OF IL6ST GENE MUTATION

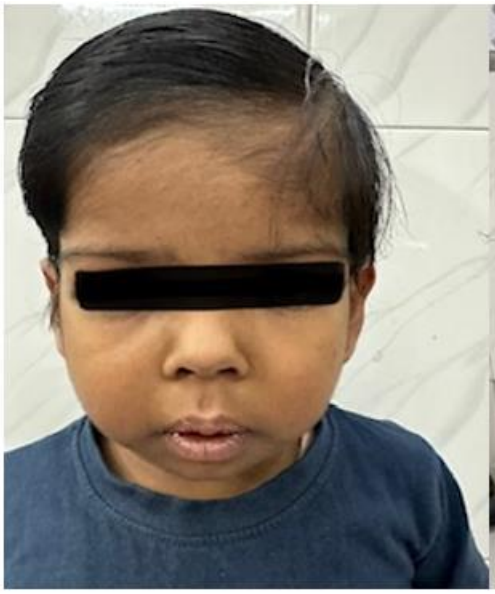
Himanshi Yadav, Dr. Anu Maheshwari

Department of Pediatrics, Lady Hardinge Medical College, India

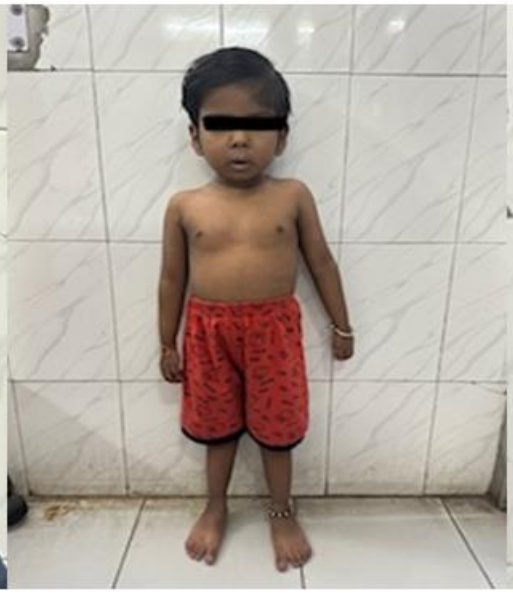
INTRODUCTION: Autosomal dominant mutation in the gene PIK3R1 can lead to Activated phosphoinositide 3 kinase delta syndrome 2(APDS2) which leads to recurrent respiratory infections, lymphoproliferation, adenopathy, splenomegaly, mild neurodevelopmental delay, decreased IgG and IgA and increased IgM levels.

CASE REPORT: A 4-year-old male child presented with complaints of swelling on the left side of neck and persistent right ear discharge for 5 months and history of recurrent loose stools since infancy. On examination, there was dysmorphic facies, pallor, bilateral submandibular lymphadenopathy, dental caries and hepatosplenomegaly. Immunoglobulin profile revealed IgA 12 (25-154 mg/dl), IGM 418 (43-196 mg/dl) and IgG-36 (463-1236 mg/dl). Lymphocyte subset analysis showed markedly reduced CD19+ lymphocytes, borderline reduction in CD3 T lymphocytes, low CD3+ CD4+ TH lymphocytes, low CD3/ CD16+ 56+ NK cells and reversal of CD3 and CD8 T lymphocytes ratio. The final diagnosis was made based on whole exome sequencing which showed autosomal dominant IL6ST gene missense mutation in exon 7 (p. Tyr257His) and an autosomal dominant mutation in PIK3R1 gene. Mother had heterozygous mutation in the IL6ST gene however she was phenotypically normal. This shows that the child had de novo PIK3R1 gene mutation and presented with features of APDS2 gene mutation along with incomplete penetrance of IL6ST gene mutation features. The patient now is on monthly IVIg infusion.

CONCLUSION: This case illustrated the possibility of expanding known APDS2 phenotype to include dysmorphic features that are not previously reported. The explanation could be associated SHORT syndrome or incomplete penetration of the IL6ST mutation.



Frontal eminence, depressed nasal bridge, maxillary prominence, anteverted nares



Picture showing Short stature

Picture showing low hairline

Comparison of our study with the reported cases	Materna-kiryluk A, et al, 2021	Index case	APDS2 syndrome reported cases
AGE OF ONSET	Neonatal period	Infancy	median age -1.7 years
GENE	IL6ST Ser187_Tyr190del	IL6ST p.TYR257His	PIK3R1 skipping of exon 11
INHERITANCE	AD	AD	AD
GROWTH	Short stature	Short stature	Growth retardation
HEAD	Prominent forehead, low hairline on the back of head Macrocephaly (HC=36CM, 90TH PERCENTILE)	prominent forehead, low hairline	microcephaly in 2 cases.
LYMPHADENOPATHY	Present occipital, cervical, supraclavicular, axillary and inguinal	cervical	Present
FACE	EYES- Hypertelorism, down slanting, EARS- low set, Macroglossia, Depressed nasal bridge	Down slanting eyes, palpebral fissures , depressed nasal bridge, anteverted nares.	Not reported
RESPIRATORY	Recurrent pulmonary infections Granulomatous lung disease Pectus carinatum	Otitis media CECT chest normal	otitis media, sinusitis, bronchitis, and pneumonitis, bronchiectasis
AUTOIMMUNITY	autoimmune cytopenia absent	Absent	Present

P-25

Rare variants of rare diseases

A CASE OF DRESS SYNDROME AND RECURRENCE

Adith Bondugula, Pritimay Pradhan, Basavaprabhu Achappa

Department of General Medicine, Kasturba Medical College, Mangalore, Manipal Academy of Higher Education, India

Background

Drug reaction with eosinophilia and systemic symptoms (DRESS) is a rare drug induced hypersensitivity reaction having cutaneous eruptions, eosinophilia, lymphadenopathy and/or internal organ involvement. Diagnosis is based on the clinical history, presenting complaints, and lab investigations. Finally, treatment is done by withdrawing the offending drug and starting steroids and IVIG. Usually, patients will not have any recurrences, but very rarely there can be a relapse. The presenting complaint will be another cutaneous eruption with organ involvement.

Case Report

A 37-year-old woman presented with erythematous pruritic rash over arms, trunk, and face; oral ulcers for 1 month, fever for 10 days. The patient previously received oral/topical immunosuppressants (leflunomide, HCQ, methylprednisolone, NSAIDS, wysolone, clobetasol, cyclosporine) for skin rash and joint aches. Patient was extensively evaluated. After clinical, laboratory, and ultrasonographic investigations, a rheumatology consult was taken, she was diagnosed with DRESS, and started on IVIG and wysolone. She improved and was discharged.

A few months later, she presented with similar symptoms, with episodes of vomiting and yellowish discoloration of eyes and urine.

Objectives

To determine causative drug
To determine recurrence

Methods

USG Abdomen- fatty liver, edema of gallbladder wall
CBC- eosinophilia
LFT: raised total and direct bilirubin, ALT and AST
Leptospira IgM and Weil-Felix: Negative
Hepatitis A and E, CMV, EBV, HHV-6: Negative
FNAC of cervical lymph nodes: Reactive lymphadenitis
Skin biopsy: Parakeratosis, mild acanthosis

Conclusion

Another rheumatology consult was ordered. Patient was diagnosed with recurrence, started on IVIG and prednisolone, and after 2 weeks she was discharged.

P-26

New treatment modalities

DRUG REPURPOSING SCREEN IN DROSOPHILA MELANOGASTER TO DEVELOP NEW TREATMENT FOR MYELOPROLIFERATIVE NEOPLASMS

Erika Gábor[1], Gábor Csordás[1], Melinda Horvát[1], Bayan Kharrat[1], Gábor Szebeni[2], **Viktor Honti**[1]

[1]*Institute of Genetics, HUN-REN Biological Research Centre, Hungary*
[2]*Laboratory of Functional Genomics, HUN-REN Biological Research Centre, Hungary*

Background:

Myeloproliferative neoplasms (MPNs) are blood cancers caused by tumorous transformation of the myeloid precursor cells located in the bone marrow. Chronic myeloid leukemia (CML), polycythemia vera (PV), essential thrombocythemia (ET) and primary myelofibrosis (PMF) are the four types of myeloproliferative neoplasms. To develop effective ways of treatment, it is crucial to understand the genetic background and the mechanisms of MPN progression as well as to discover potential new drug candidates.

Objectives:

We aim to discover and test new therapeutic agents that can be utilised to treat MPNs, as well as to gain insight into the mechanisms of disease progression.

Methods:

Drosophila provides a versatile system to investigate MPNs in detail. We use Drosophila MPN models in combination with human cell lines in high-throughput repurposing screens that aim to identify potential new therapeutic agents.

Results:

We isolated several new drug candidates, which are currently being tested in human cell cultures to validate their therapeutic usability. Those drugs that showed specific effects in immortalized cell lines will be tested in primary samples isolated from MPN patients.

Conclusion:

Our results prove that Drosophila is a valuable model to discover new drugs against myeloproliferative diseases. We hope that our findings will contribute to MPN therapy in the near future.

The National Laboratory of Biotechnology was supported by the Hungarian National Research, Development and Innovation Office—NKFIH through the grant No. 2022-2.1.1-NL-2022-00008.

P-27

Raising awareness for rare diseases

For The RARE–Please Take CARE

Bhavna Dhingra[1], Garima Goel[2], Prashant Chaware[3], Ranu Tripathi[1]

[1]*Pediatrics, Aiims, India*
[2]*Pathology and Lab Medicine, Aiims, India*
[3]*Anatomy, Aiims, India*

Background
The collective impact of Rare Diseases is huge affecting 6-8% of population globally. There is limited awareness about these disorders as clinical manifestations of most of these disorders are non- specific and overlapping with common illnesses. Lack of awareness amongst health care professionals and non-availability/accessibility of diagnostic modalities lead to these disorders being missed or misdiagnosed. This leads to lack of robust epidemiological data about exact prevalence and geographical distribution of these conditions.

Objectives
1. To raise awareness about Rare diseases like hemoglobinopathies, muscular dystrophy and lysosomal storage disorders among health care professionals and lay people.

2. To create awareness about availability of option for prenatal diagnosis for families having affected individuals with rare diseases.

Methods
1. Created a state level Rare Disease Working Group with participants from all medical colleges in the state and state health authorities.

2. Celebrated Rare disease day and Newborn Screening awareness month with involvement of UG, PG, Nursing staff, students and patient families.

3. Conducted National Level CME on Rare Diseases in hybrid mode for nationwide participation.

Results
Increase in number of referrals from peripheral centres to tertiary care hospital Genetics clinic.
Diagnosis established and enzyme replacement therapy initiated for three patients with LSDs and few patients enrolled in ongoing trials for muscular dystrophy.
Increased numbers of women undergoing prenatal diagnostic techniques.

Conclusions
1. Comprehensive management of rare diseases requires concerted efforts for increasing awareness about these disorders, capacity building initiatives for improved accessibility and availability of diagnostic facilities and trained manpower.

2. Collaborative efforts of all stakeholders including patients, policy makers and healthcare professionals are the need of the hour to generate robust epidemiological data about these disorders and redirect appropriate allocation of resources for research and development of affordable therapeutic alternatives.

P-28

Relations between rare diseases and common disorders

OCCURRENCE OF RARE MYOPATHIES IN OUR OUTPATIENT PRACTICE - THE EXPERIENCE OF A HUNGARIAN RARE DISEASE CENTER

Boglarka Brugos, György Pfliegler

Internal Medicine Division of Hematology and Rare Diseases, University of Debrecen, Hungary

Background

Muscle weakness, -pain, -atrophy,-fatigue, and numbness of the legs are frequent symptoms among patients visiting our Rare Disease Outpatient Service. Most of them have already undergone a lot of investigation without a definitive diagnosis.

Objective

In the past five years (2018-2023) we have examined 28 patients with the symptoms mentioned above, in 15 cases we performed muscle biopsy with detailed histopathological and electron microscopic examination.

Results

Based on histopathological examination inflammatory myopathy, mitochondrial disease, endocrine and amyloid musculopathy were diagnosed. In some cases, genetic testing was also done. In a young 21 years old patient a new, so far unknown mutation was diagnosed in DYSF (dysferlin) gene, a similar mutation was detected previously in a patient with limb-girdle muscle dystrophy. Dysferlinopathy, an autosome recessive disorder, includes a spectrum of myopathies causing muscle weakness and atrophy, having two major and two minor phenotypes.

Conclusions

In our presentation, we summarize the data of our patients with myopathies, with a special focus on the difficulties of differential diagnosis and the importance of a thorough collaboration with pathologists, and genetists.

P-29

New treatment modalities

ENHANCING BILIARY STRUCTURE IDENTIFICATION USING PERCUTANEOUS CHOLECYSTOSTOMY DRAIN DELIVERY OF INDOCYANINE GREEN: A GLOWING TWO CASE REVIEW

Peter Alexander[1], **Vincent Marcucci**[2], Patricia Torres[2], Vincent Marcucci[2], Dena Arumugam[2]

[1]*School of Medicine, St. George's University Medical School, Grenada*
[2]*Surgery, Jersey Shore University Medical Center, USA*

Introduction: Intraoperative cholangiography using fluorescent indocyanine green (ICG) excretion into bile is a non-invasive, safe, and cost-effective technique used to identify biliary anatomy and prevent bile duct injury. In this retrospective two-case report, two patients with mature percutaneous cholecystostomy drainage catheters (PCDC) underwent interval robot-assisted laparoscopic cholecystectomies with administration of ICG via PCDC. The aim of this study is to explore the advantages of biliary anatomy visualization using PCDC as a route to administer ICG as a means of reducing bile duct injury.

Case Presentation: Two patients with percutaneous drainage catheters were studied. ICG solution (2.5 mg in 10 mL of sterile saline) was administered intracystically via percutaneous cholecystostomy drain within 1 hour of the operative start time. The biliary anatomy was confirmed using FireFly imaging and no additional intraoperative near-infrared fluorescent enhancement seen outside of the biliary anatomy. The gallbladders were excised and removed using an Endo Catch bag through the umbilical trocar.

Discussion: There are several advantages of this technique including cost-effectiveness, availability, overall safety of the compound, and no additional need for further equipment. The disadvantages after administration may include a biliary obstruction limiting the spread of ICG, and leakage of ICG into the peritoneal cavity resulting in the loss of biliary enhancement. In this case series, the biliary tree was visualized in 100% of cases where ICG was injected directly into the gallbladder compared to 83% using intravenous injection in prior literature. We used the intracystic injection of ICG to bypass hepatic structures in an attempt to reduce the background fluorescence and increase the contrast of biliary structures from surrounding tissue. Accurately and reliably identifying structures during the dissection and critical view of the gallbladder will reduce the risk of inadvertently injuring the biliary structures.

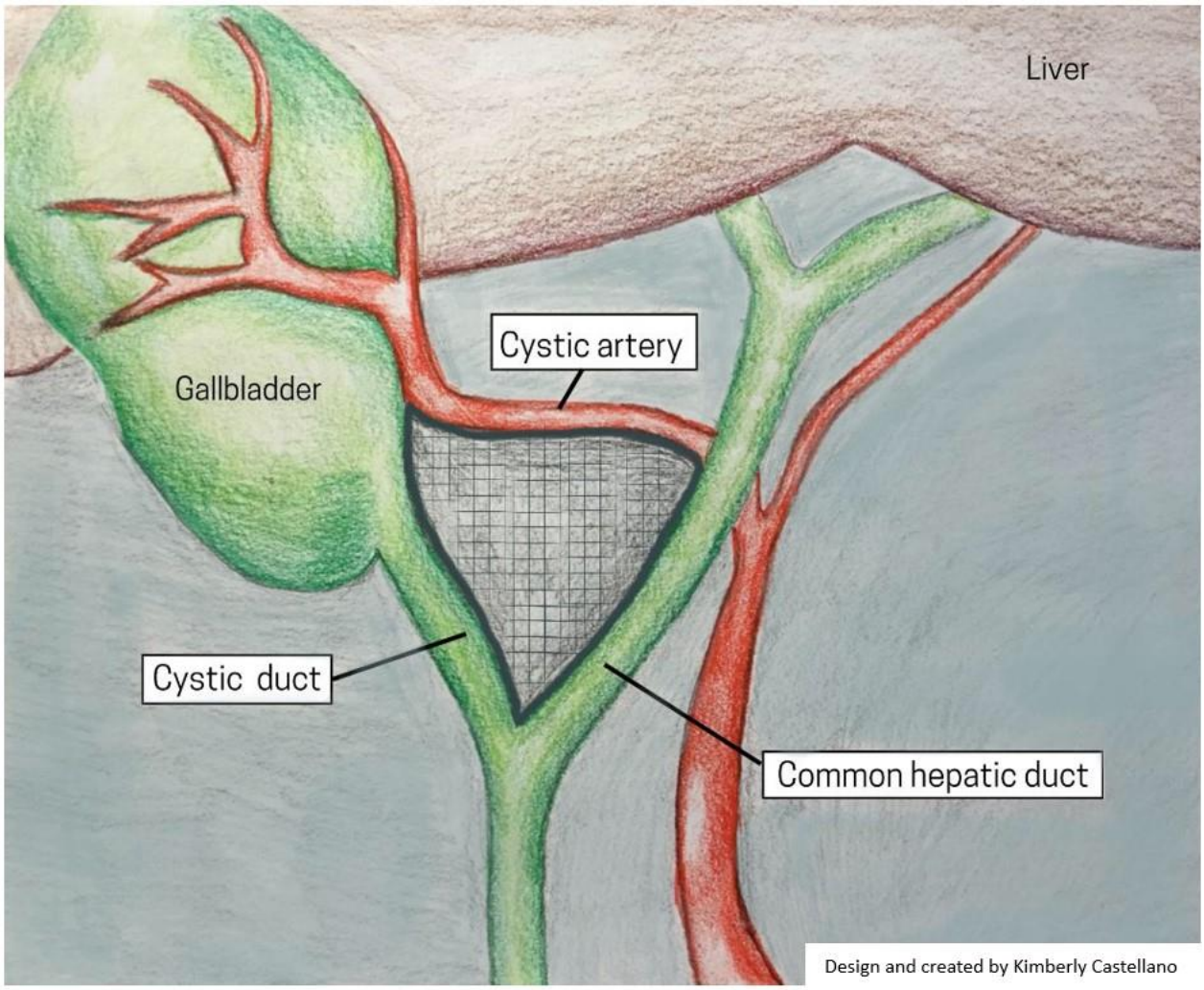


Figure 1. Illustrative depiction of Calot Triangle.

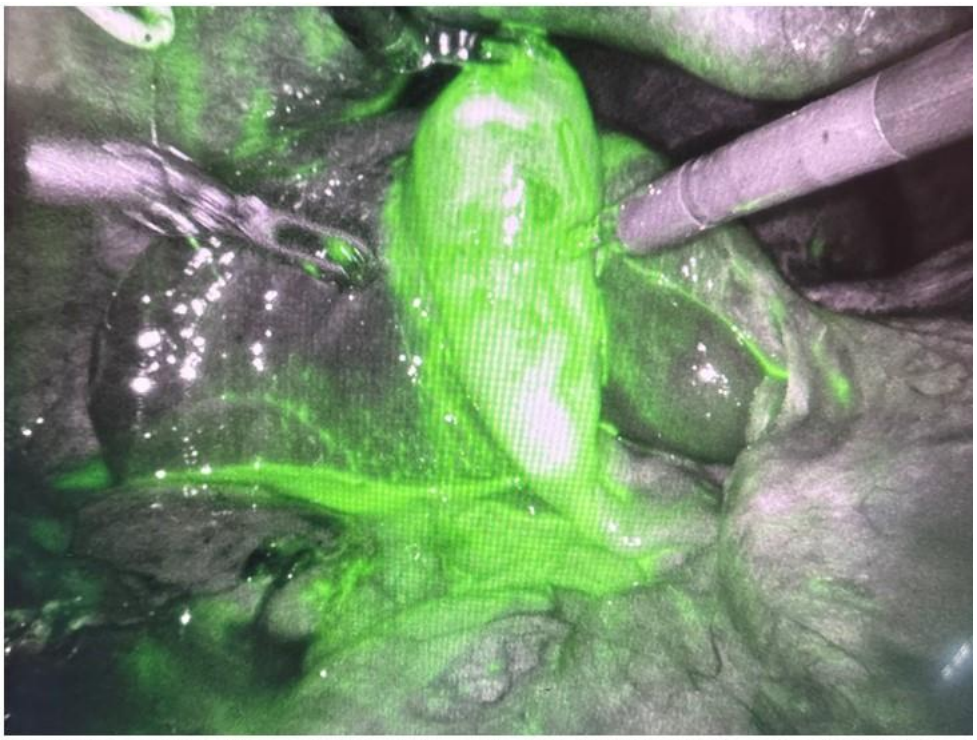


Figure 2. Laparoscopic near-infrared cholangiogram status post intracystic administration of ICG.

P-30

Miscellaneous rare diseases

LYMPHOCYTIC HYPERPLASTIC TRACHEOBRONCHITIS AS A LIFE-THREATENING DISEASE

Efthymia Papadopoulou[1], Chrisoforos Proimos[1], Ioannis Dimitiradis[2], Konstantinos Katsoulis[3], Stavros Tryfon[1]

[1]*Pulmonary, "G. Papanikolaou" Gen. Hospital, Thessaloniki, Greece, Greece*
[2]*Pathology, "G. Papanikolaou" Gen. Hospital, Thessaloniki, Greece, Greece*
[3]*Respiratory, 424 Army General Hospital, Greece*

Background

Airway diseases involve heterogeneous pathophysiological pathways in genetically predisposed individuals with potential life-threatening exacerbations.

Objectives

To present a rare challenging case of lymphocytic hyperplastic tracheobronchitis, that has not been described before.

Methods

A 53-year-old male presented with severe respiratory distress, unable to complete sentences due to air trapping. Progressive breathlessness had emerged one year ago with inspiratory and expiratory wheezing in the context of a deteriorating airway obstructive disorder (FEV1/FVC 31.8, FEV1 21% from 76%predicted during one year), unresponsive to inhaled or per-os corticosteroids and long-acting beta-2 agonists. The upper airway appeared normal in endoscopy, without vocal cord dysfunction. His medical history included gastroesophageal reflux disease and exposure to organic compounds at a fast-food restaurant with a non-remarkable family history. Differential diagnosis comprised asthma, vasculitis, malignancy, amyloidosis, pulmonary lymphoproliferative diseases, tracheobronchopathia osteochondroplastica and relapsing polychondritis.

Results

A chest computed tomography revealed concentric stenosis of the trachea and main bronchi. Bronchoscopy confirmed diffuse mucosal thickening and severe concentric stenosis. Histological examination revealed lymphocytic aggregation, without neoplastic cells nor Ki67 expression. Congo red stain and serum immunological markers were negative. In the absence of an established diagnosis, the patient received rescue therapy targeting the mucosal lymphocytic infiltration (rituximab courses) showing immediate clinical improvement with remission of wheezing and respiratory distress. At a 2 year follow-up, FEV1 improved significantly (39%pred) and bronchoscopy revealed partial remission of stenosis, with scarce lymphocytic infiltration, while no other disorder has emerged.

Conclusion

Lymphocytic hyperplastic tracheobronchitis is an orphan disease. Clinical awareness is essential to identify rare airway diseases warranting urgent therapeutic management.

P-31

General challenges in rare disease

THE ROLE OF CD25 AS POTENTIAL MARKER FOR PATHOGENESIS AND RESPONSE TO THERAPY IN IDIOPATHIC PULMONARY FIBROSIS PATIENTS

Gaia Fabbri, Matteo Fanetti, Maddalena Messina, Martina Armati, Elena Pordon, Beatrice Perea, Vittoria Ventura, Lorenzo Alderighi, Lucia Cassai, Magda Viani, Marco Guerrieri, Martina Meocci, Sara Croce, Tommaso Pianigiani, Giusi Montuori, Benedetta Picchi, Guillaume Starnini, Matilde Pengue, Akter Dilroba, Michele Genovese, Simona Luzzi, Stefano Cattelan, Francesco Dioguardi, Paolo Cameli, Laura Bergantini, Elena Bargagli, Miriana D'alessandro

Department of Medical and Surgical Sciences and Neurosciences, University of Siena, Italy

Background: Idiopathic pulmonary fibrosis (IPF) is a progressive interstitial lung disease. IPF aetiology is still not clear and regulatory T cells (T-reg,CD4+CD25+CD127-) are involved in its pathogenesis. Extracellular vesicles (EVs) are secreted by cell membrane within body fluids.

Our study aimed to characterize the serum-EVs-surface CD25-expression from IPF patients and to validate such marker in bloodstream of IPF patients after antifibrotic therapy.

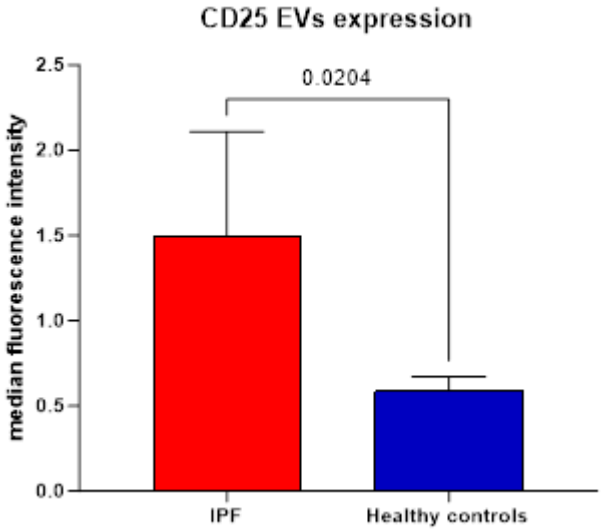
Materials and methods: Twenty-four IPF patients monitored at Siena Referral Centre for rare lung disease were retrospectively enrolled. Serum CD25-EVs-expression were identified through flowcytometry. Fourteen IPF patients were selected for T-reg analysis and they followed-up for at least 12 months after nintedanib-therapy. Ten healthy controls (HC) were also enrolled.

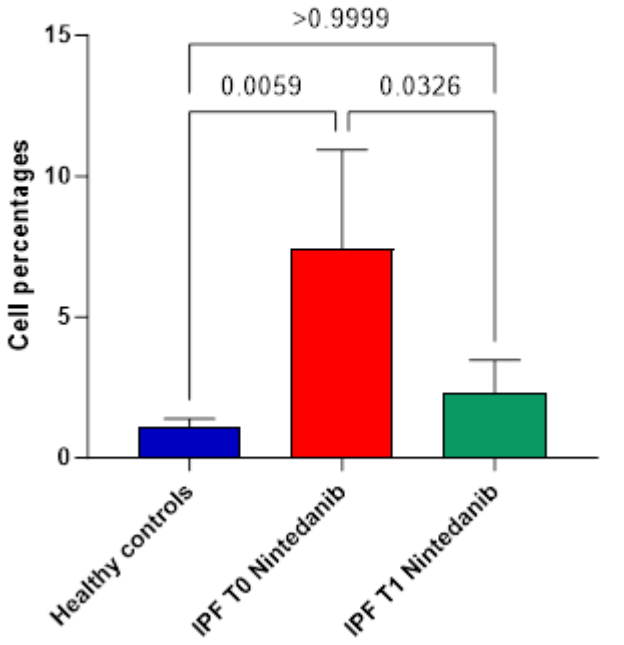
Results: CD25-expression were abundant on EVs-IPF than EVs-HC ($p=0.0204$). An increase in T-reg percentages in IPF than HC group ($p=0.0059$). Comparative analysis showed higher T-reg proportions before (T0) treatment than those after (T1) therapy ($p=0.0326$).

Discussion: In this preliminary analysis we identified an increase of CD25-EVs-expression in IPF patients than HC.

Accordingly, we deep investigated the CD25-expression on PB showing a significant increase T-reg percentages in IPF than HC, as well as before and after nintedanib. Additionally, we identified similar T-reg percentages in HC and IPF-T1 demonstrating a restoring of such cells after antifibrotic therapy.

In conclusion, this study shines a spotlight on the understanding of CD25 in the pathogenesis of IPF and the role of T-reg as a potential biomarker of response to antifibrotic therapy.


CD25 EVs expression
median fluorescence intensity
2.5
2.0
1.5
1.0
0.5
0.0
0.0204
IPF
Healthy controls


T-reg (CD4+CD25+CD127-) proportions
Cell percentages
15
10
5
0
>0.9999
0.0059
0.0326
Healthy controls
IPF T0 Nintedanib
IPF T1 Nintedanib

P-32

Single gene diseases

A NOVEL HOMOZYGOUS MISSENSE VARIANT IN THE SLC29A3 GENE CAUSES OVERLAPPING FEATURES OF FAMILIAL ROSAI-DORFMAN DISEASE AND H SYNDROME

Antonella Pizza[1], Margherita Scarpato[1], Roberta Zeuli[1], Claudia Esposito[2], Marcella Contieri[2], Vincenzo Nigro[1,3], Silverio Perrotta[2], Immacolata Tartaglione[2]

[1]*Department of Precision Medicine, University of Campania "Luigi Vanvitelli", Italy*
[2]*Department of Women's and Children's Health and General and Specialized Surgery, University of Campania "Luigi Vanvitelli", Italy*
[3]*Telethon Institute of Genetics and Medicine, (TIGEM), Italy*

The histiocytosis-lymphadenopathy plus syndrome includes 4 histiocytic disorders: Faisalabad histiocytosis, familial Rosai-Dorfman disease (RDD), H syndrome and pigmented hypertrichosis with insulin-dependent diabetes. They are caused by homozygous or compound heterozygous pathogenetic variants in the SLC29A3 gene, encoding the human equilibrative nucleoside transporter 3, which maintains the intracellular pool of nucleosides. Even if each disorder is characterized by its own clinical presentation, overlapping features are described in literature. In view of the shared genetic and phenotypic manifestations, they can be regarded as SLC29A3 spectrum disorders.

Here we report a 15-year-old girl who presents hyporegenerative anemia, autoimmunity-related problems like flexion contractures of the proximal interphalangeal joints and insulin-dependent diabetes, painless cervical lymphadenopathy, hepatosplenomegaly, vision loss, short stature, hallux valgus with polyclonal hypergammaglobulinemia, increased inflammatory markers and positive antinuclear antibody in laboratory tests. Clinical exome sequencing detected a missense variant c.914CG p.(Thr305Arg) in exon 6 of the SLC29A3 gene, homozygous in the proband and heterozygous in her parents. The variant has not been reported in literature neither in control databases and is predicted as unknow significance. Even if it is a novel variant, the exon 6 is a recurrent localization of nucleotide change in the SLC29A3 gene.

This case provides an evidence supporting the wide phenotypic variability of SLC29A3 disorders: features of both RDD and H syndrome are here associated, without the distinctive dermatological hallmarks of the H syndrome. It also suggests the crucial role of genetic analysis in diagnosing complex clinical presentations and expands the genotype landscape of the SLC29A3 disorders.

P-33

New treatment modalities

HUMAN DISEASE MODELLING: KEY CONTRIBUTION OF INFRAFRONTIER TO RARE DISEASE RESEARCH

Gema Valera[1], Montse Gustems[1], Sabine Fessele[1], Asrar Ali Khan[1], Michael Raess[1], Martin Hrabê de Angelis[1,2]

[1]*INFRAFRONTIER GmbH, INFRAFRONTIER, Germany*
[2]*Institute of Experimental Genetics, Helmholtz Zentrum München, Germany*

Background: With over 7,000 rare diseases (RDs) affecting an estimated 30 million people in Europe, the need for RD research and knowledge is paramount. These conditions present significant medical challenges. Fortunately, the EU supports collaborative initiatives to address RD research.

Objectives: INFRAFRONTIER, the European Research Infrastructure for Modelling Human Diseases, plays a crucial role in advancing research on RDs. Our primary goal is to provide essential resources and services to fundamental and preclinical researchers, accelerating the investigation of these conditions.

Methods: Leveraging a network of over 20 partner institutions, we offer valuable services, including systemic phenotyping and mouse model generation, all of which adhere to rigorous standards to deliver the highest quality. Our dedication to *in vivo* models complements our progressive transition toward *in vitro* models, ensuring INFRAFRONTIER evolves and aligns with Europe`s road map.

Results: INFRAFRONTIER maintains a thriving global community of users and collaborators. Together, they have both benefited from and contributed to our growing repository of mutant mouse lines, notably via the European Mouse Mutant Archive (EMMA). At present, our archive boasts more than 2,200 mouse strains associated with over 1,600 RDs.

Conclusion: INFRAFRONTIER stands as a valuable Research Infrastructure in the field of RDs. This is underscored by the extensive number of scientific publications that recognize our services and resources as fundamental to RD research. Our commitment to continuous growth and adaptation, coupled with our expanding *in vitro* capabilities, solidifies INFRAFRONTIER`s role as a vital contributor to the advancement of RD research in Europe and beyond.

P-34

Patients focused aspects in rare diseases

GROWDMD: AN INTERNATIONAL STUDY ON TRANSITION OF YOUTH WITH DUCHENNE MUSCULAR DYSTROPHY (DMD)

Thorsten Langer[1], Sebastian Friedrich[1], Gudrun Reeskau[2], Sunil Rodger[1], Jana Willems[1], Gloria Antonini[3], Beatrice Brigliadori[4], Erika Guastafierro[4], Matilde Leonardi[4], Alessia Marcassoli[4], Isabella Moroni[4], Nardo Nardocci[4], Giada Perinel[3], Anna Petruzza[3], Anne Fournier[5], Julia Frei[6], Jan Willem Gorter[6], Rocio Gutierrez Rojas[5], Olaf Kraus De Camargo[6], Dayle McCauley[6], Homira Osman[7], Kinga Pozniak[6], Nethmi Rajapakse[6], **Anna Swain**[6]

[1]*N/a, Universitätsklinikum Freiburg, Germany*
[2]*N/a, Deutsche Gesellschaft für Muskelkranke e.V., Germany*
[3]*N/a, Parent Project APS, Italy*
[4]*N/a, Fondazione IRCCS Istituto Neurologico Carlo Besta, Italy*
[5]*N/a, CHU Sainte-Justine Montréal, Canada*
[6]*N/a, CanChild – McMaster University, Canada*
[7]*N/a, Muscular Dystrophy Canada, Canada*

Background/Objectives: Care pathways for transition from childhood to adulthood is a well-described phenomenon, however, the transition of patients with Duchenne muscular dystrophy (DMD) is still neither well-described nor defined and organized at international level with common and agreed pathways and indicators. The international GrowDMD study aims to explore the diverse experiences of young people living with DMD and their families in Canada, Germany, and Italy to answer the questions: 1. How do patients with DMD and their caregivers experience the transition of care? 2. What measures and strategies are currently implemented in the care organizations of participating countries to support and facilitate the transition of care? 3. How can the transition of care be improved?

Methods/Results: This study utilizes an integrated knowledge translation process and is guided by the World Health Organization frameworks. Using a mixed methods design, this study consists of three phases across participating countries in English, French, German and Italian: Scoping review of the literature and semi-structured interviews with young individuals living with DMD, their caregivers, and service providers to explore the transition of care experiences; Qualitative surveys informed by findings from the interviews to determine priorities for improvement in each country, and focus groups to identify potential solutions; Development of knowledge translation products.

Conclusion: The integrated nature of this project will allow us to co-create with patients, families, and clinicians a set of general recommendations, tailored to local contexts, that can serve as a model for the transition care path of patients with DMD.

P-35

Raising awareness for rare diseases

5 YEARS OF EUROPEAN REFERENCE NETWORK FOR RARE INHERITED AND CONGENITAL ANOMALIES (ERNICA)-DRIVEN CROSS-BORDER CARE FOR RARE DISEASES

Rebecca Pulvirenti[1,2], Iris den Uijl[2], Rene Wijnen[3], Francesco Fascetti-Leon[1]

[1]*Pediatric Surgery Unit, Department of Women's and Children's Health, Padua University Hospital, Italy*
[2]*ERNICA Project Manager, Erasmus University Medical Center, Netherlands*
[3]*Department of Pediatric Surgery and Intensive Care, Erasmus University Medical Center - Sophia Children's Hospital, Netherlands*

BACKGROUND AND OBJECTIVES:

Since 2017, the European Reference Networks (ERNs) have been working towards an improved cross-border care for patients with rare diseases. In this regard, the European Reference Network for rare Inherited and Congenital Anomalies (ERNICA) actively supported clinicians' research initiatives and encouraged their use of the Clinical Patient Management System (CPMS) for complex clinical case discussions. As coordinators of the eHealth work package we faced several challenges to adjust network's requirements to clinicians' resources, identifying the lack of protected time as a primary reason for their disengagement.

METHODS:

Over the past 5 years we explored ways to maximize ERNICA members' enthusiasm for this innovative approach to sharing clinical information, stressing the benefits of a General Data Protection Regulation (GDPR)-compliant sharing of knowledge and expertise. With the new ERNs quinquennium about to start, we summarized the criticisms gathered from members so far.

RESULTS:

ERNICA-driven research initiatives have been embraced by most of the network's members, owing to experts' willingness to collaborate and methodological support. Conversely, clinical commitment has been hampered by both the complexity of the CPMS interface and the imperative to use it beyond working hours. The absence of acknowledgment of the network activities as part of clinical duties (with dedicated time or working tasks) has also been a hindrance.

CONCLUSION:

As the ERNs project advances and expands, sustainability remains a key issue. Aligning European policies with clinicians' daily activities and achieving greater local and national recognition for healthcare provider members' efforts in cross-border care are essential.

P-36

Rare syndromes

MICRORNA EXPRESSION IN CREBBP/EP300-NEGATIVE AND POSITIVE RUBINSTEIN-TAYBI SYNDROME: A CROSS-SECTIONAL STUDY

Keano Samaritakis
Research & Development, ToxGenSolutions, Netherlands

Background:
Rubinstein-Taybi Syndrome (RTS) is a rare genetic disorder with a prevalence of 1 in 100,000-125,000 individuals, leading to various clinical manifestations. The syndrome is primarily associated with mutations in the CREBBP and EP300 genes. However, an estimated 60-70% of phenotype-positive RTS individuals lack these genetic markers. Moreover, extensive downregulation of genes involved in RNA/DNA metabolic processes suggests that RTS arises from chromatin dysregulation, reflected in broad transcriptional disturbances.

Objectives:
This investigation aims to examine microRNA (miRNA) expression landscapes in phenotype-positive RTS individuals with and without CREBBP/EP300 mutations, to identify functional relationships and unrecognized implicated genes. Additionally, the study explores potential therapeutic strategies targeting this condition.

Methods:
A cohort comprising phenotype-positive CREBBP/EP300 mutation-positive individuals, phenotype-positive yet mutation-negative RTS subjects, and age- and sex-matched healthy controls will be established using a cross-sectional study design. Stringent ethical protocols, including informed consent and data protection measures, will be implemented. Analyses will encompass differential miRNA expression studies and microRNA-mRNA interaction analyses.

Results:
Anticipated findings may reveal differential miRNA expression patterns that could serve as preliminary diagnostic profiles for RTS, stimulating further research into miRNA-based diagnostic approaches.

Conclusion:
The study aims to identify potential genetic candidates, miRNA profiles, and therapeutic targets for RTS, with potential impacts on patient care and drug development, adhering to high standards of scientific inquiry.

P-37

New treatment modalities

IMMUNOTHERAPY SAFE AND EFFECTIVE THERAPY FOR MELANOMA ASSOCIATED RETINOPATHY

Christopher Hueser[1,2], Nisha Hueser[3]

[1]*Oncology/Hematology, Mercy, USA*
[2]*Oncology/Hematology, Hueser Medical Consulting, USA*
[3]*Research, Hueser Medical Consulting, USA*

Background

Melanoma-associated retinopathy (MAR) is a rare paraneoplastic syndrome typically with rapid onset of visual changes. Any type of melanoma may be associated with MAR and symptoms may precede or follow the diagnosis of melanoma. Patients with MAR have the same antigenic retinal proteins that have been associated with cancer-associated retinopathy. Therapies utilized for MAR have been cytoreduction of metastatic disease through metastasectomy, chemotherapy, radiation and intravenous immunoglobulin. For refractory visual symptoms, additional therapies include systemic corticosteroids and plasmapheresis, but with limited success. A 69-year-old female with a previously excised left medial calf melanoma and no adjuvant therapy began to develop bilateral visual changes with purple and green wavy lines. Positron emission tomography (PET) revealed a hypermetabolic left inguinal lymph node. Biopsy revealed recurrent melanoma. Serologic evaluation demonstrated anti bi-polar cell antibody positivity. Treatment with corticosteroids and intravenous immunoglobulin did not relieve her symptoms. Subsequent treatment with nivolumab resulted in normalization of her PET scan, anti bi-polar antibody negativity and resolution of her symptoms. We describe a 69-year-old patient with MAR who obtained a complete response after eight cycles of treatment with nivolumab. She tolerated therapy without immune related side effects and remains symptom free.

Objectives

To describe the effectiveness of nivolumab in the treatment of melanoma associated retinopathy.

Methods

Serial positron emission tomography, serial anti bi-polar antibody testing.

Results

Resolution of PET imaging, negativity of her anti bi-polar antibody testing and resolution of her symptoms.

Conclusion

Nivolumab appears to be a safe and effective treatment for MAR.

P-38

Raising awareness for rare diseases

BIRT-HOGG-DUBÉ (BHD) SYNDROME IN PATIENTS WITH SPONTANEOUS PNEUMOTHORAX (SP). PRELIMINARY RESULT OF A DUTCH MULTICENTER STUDY SHOWS HIGH PREVALENCE OF BHD IN SP PATIENTS

B P Hoppe[1], J W K Van Den Berg[2], W Thijs[3], S Smulders[4], SRS Ramai[5], HJ Smit[6], D Schippers[7], FMNH Schramel[8], W J Blox, M Nagtegaal[10], RN Van Rossem[11], LJM Kroft[1], JL Stoger[1], F Baas[1], CJ Van Asperen[1], CL Klop[1], PE Postmus[1]

[1]*Pulmonology, Leiden University Medical Center, Netherlands*
[2]*Pulmonology, Isala, Netherlands*
[3]*Pulmonology, NWZ, Netherlands*
[4]*Pulmonology, Jeroen Bosch Ziekenhuis, Netherlands*
[5]*Pulmonology, Alrijne Ziekenhuis, Netherlands*
[6]*Pulmonology, Rijnstate, Netherlands*
[7]*Pulmonology, Haga Ziekenhuis, Netherlands*
[8]*Pulmonology, Sint Antonius Ziekenhuis, Netherlands*
[10]*Pulmonology, Groene Hart Ziekenhuis, Netherlands*
[11]*Pulmonology, Reinier De Graaf Gasthuis, Netherlands*

Introduction:

Investigation to diagnose Birt-Hogg-Dubé (BHD) syndrome in primary spontaneous pneumothorax (PSP) patients is not routine despite the possibility of a prevalence of BHD as high as 3.4-10 percent1,2,3. The lifetime risk in BHD patients for renal cell cancer is high (up to 35%)4 and may therefore justify screening for BHD in PSP patients. Furthermore, for each affected SP patient 3-4 affected family members were found. Screening might therefore result in detecting 4- 5 new patients at high risk of developing renal cell cancer per PSP patient.

Objectives:

The aim of this study is to establish the prevalence of BHD syndrome in patients presenting with a ‘primary’ SP. The second aim of the study is to detect other abnormalities likely related to the SP. In this study a total of 350 patient will be included from 11 hospitals in the Netherlands.

Methods:

Patients with a PSP are tested for the existence of BHD through FLCN mutation testing and low dose CT Thorax. In addition a questionnaire at start, 1 and 4 years is performed. We present the preliminary results of screening for BHD in PSP patients.

Results:

From September 2020 till August 2023 229 spontaneous pneumothorax patients were included and analyzed in this study. Nine (4%) patients were found to carry a FLCN mutation. The number of affected family members is not yet known.

Conclusion:

These early findings suggest that the prevalence of BHD in SP patients might be as high as 4 percent. As the lifetime risk in BHD patients for renal cell cancer is high, and through each affected person asymptomatic family members may be found, this justifies screening for BHD in SP patients.

References:

1. Ren, H.Z. et al. Clin Genet 2008; 74: 178-1832.
2. Johannesma PC et al Eur Respir J 2015; Apr;45 (4):1191-4
3. Shiram JD et al. BMC Pulm Med. 2022; Aug 26;22(1):325
4. Schmidt, L.S. et al. Semin Oncol. 2016; 43: 566–574

P-39

New treatment modalities

PRIMARY HYPEROXALURIA TYPE 1 TREATED WITH LUMASIRAN IN A SEVERE CHRONIC KIDNEY DISEASE ADULT PATIENT

Elena Emanuela Rusu[1,2], Corina Pislaru[3], Alexandru Iordache[4], Dorina Tacu[5], Robert Pandele[1], Simona Ioanitescu, Andreea Blaga[1], Raluca Bobeica[2], Gener Ismail[1,2]

[1]*Fundeni Clinic of Nephrology, "Carol Davila" University of Medicine and Pharmacy, Romania*
[2]*Department of Nephrology, Fundeni Clinical Institute, Romania*
[3]*Nephrology, Diaverum Focsani Nephrology and Dialysis Medical Center, Romania*
[4]*Clinic of Urology, Fundeni Clinical Institute, Romania*
[5]*Clinic of Urology and Renal Transplant, Fundeni Clinical Institute, Romania*

Background

Primary hyperoxaluria type 1 (PH1) is a devastating genetic metabolic disorder characterized by excessive production and accumulation of oxalate which leads to kidney stones, nephrocalcinosis, and chronic kidney disease (CKD). Lumasiran is a novel small interfering RNA therapy which decreased the hepatic oxalate production that has been recently approved for the treatment of PH1.

Objectives

We present the case of a 41-year-old female patient with bilateral nephrolithiasis and nephrocalcinosis and severe CKD diagnosed with PH1.

Methods and Results

The patient past medical history includes hematuria at 6 years when a bladder stone was revealed, multiple episodes of spontaneous kidney stone passage, and a percutaneous nephrolithotomy intervention. The patient aggravated her CKD during and after a pregnancy and was referred to nephrologist. Metabolic evaluation followed by genetic test has been performed. PH1 was confirmed by the presence of two pathogenic mutations in the AGXT gene. The patient was completely evaluated in a multidisciplinary team and received standard treatment plus lumasiran. The patient had a rapid and sustained decrease in urinary oxalate (UOx) and plasma oxalate (POx), with a mean reduction after lumasiran administration of about 85% for UOx and about 60% for POx. During the follow-up period, eGFR remained stable at about 20 ml/min/1.73 m2, and no new kidney stones were observed.

Conclusion

In our PH1 patient with severe CKD severely, lumasiran proved to be very effective in rapidly and reducing UOx and POx to near-normal levels, while kidney function remained stable.

P-40

Single gene diseases

RARE ABCA4-ALLELE BECOME COMMON IN FAMILIES WITH MULTIPLE MACULAR PHENOTYPES

Kunka Kamenarova[1,2], Sylvia Cherninkova[3], Kalina Mihova[1,2], Krasimir Koev[4], Bilyana Mihaylova[5], Ivaylo Tournev[3], Radka Kaneva[1,2]

[1]*Molecular Medicine Center, Department of Medical Chemistry and Biochemistry, Medical University- Sofia, Sofia, Bulgaria*
[2]*Laboratory of genomic diagnostics, Department of Medical Chemistry and Biochemistry, Medical University-Sofia, Sofia, Bulgaria*
[3]*Department of Neurology, University Hospital Alexandrovska, Medical University-Sofia, Sofia, Bulgaria*
[4]*Ophthalmology, Clinic Senter St. Joan Rilski, Plovdiv, Bulgaria*
[5]*Ophthalmology, Vision Clinic, Sofia, Bulgaria*

Background: Pathogenic variants in the ATP-binding cassette, sub-family A, member 4 (ABCA4) gene are the underlying molecular cause of a large and complex group of autosomal-recessive retinopathies ranging from early onset and fast progressing cone-rod dystrophy and retinitis pigmentosa-like phenotypes to very late onset cases of mostly mild disease sometimes resembling, and confused with, age-related macular degeneration. The high carrier frequency of pathogenic ABCA4-alleles in the general population (~1:20) often results in pseudo-dominant inheritance patterns further complicating the diagnosis and characterization of affected individuals.

Objectives: To describe a genotype-phenotype analysis of Bulgarian Roma families with multiple macular disease phenotypes spanning across generations and segregating three distinct ABCA4 mutant alleles.

Methods: We performed targeted next-generation sequencing of clinical exome in 11 patients from 7 unrelated pedigrees. To further explore the inheritance pattern of identified ABCA4-mutations, we tested total of 62 family members using Sanger segregation analysis.

Results: We identified three pathogenic ABCA4-variants, among which c.5917delG (p.Val1973Terfs) was the most frequent representing over 50%, while p.Gly1961Glu and p.Glu1087Lys represented 15.2% and 8.5%, respectively. ABCA4-c.5917delG seen in both homozygous and compound heterozygous state with one of the other two mutation, is present in population databases (7 alleles out of 250,712; gnomAD MAF 0.02%).

Conclusion: The most prevalent variant, the change c.5917delG, was found in our cohort in 52% of all solved ABCA4-patients, which is the highest frequency reported for this mutation thus far. Additionally, we identified three families displaying a pseudo-dominant mode of inheritance, suggesting a high frequency of ABCA4-c.5917delG within this population.

P-41

Rare syndromes

HYPER IGE SYNDROME MASQUERADING AS ELEPHANTIASIS AND NON-HEALING ULCER

Bhavna Dhingra[1], Pooja Soni[1], Nehil Nigam[1], Ujjawal Khurana[2], Yogendra Yadav[1], Narendra Chaudhary[1], Umair Bargir[4], Karuna Tadepalli[3]

[1]*Pediatrics, All India Institute of Medical Sciences, India*
[2]*Pathology and Lab Medicine, All India Institute of Medical Sciences, India*
[3]*Microbiology, All India Institute of Medical Sciences, India*
[4]*Pediatric Immunology and Leukocyte Biology, Niih, India*

Background

Inborn errors of immunity are a heterogenous group of disorders which may present with life-threatening infections in infancy or later. Hyper-IgE syndrome (HIES) is a rare group of autosomal recessive primary immunodeficiency caused by tyrosine kinase 2 gene (TYK2) and cytokinesis 8 (DOCK8) mutations (more common). It is characterized by recurrent bacterial and viral infections, atopic eczema, and raised serum IgE levels.

Objectives

16 month old male, presented with a pustule in left axilla at 6-8 weeks of age, after BCG vaccination. There was Insidious onset of erythematous swelling over right knee at 3months of age. Progressively increased to elephantiasis like swelling in right lower limb along with plaque/blister formation, spreading up to trunk along with persistent fever. Child received Antitubercular treatment due to suspicion of disseminated BCGosis.

Methods

Complete blood count revealed leukocytosis with persistent eosinophilia (Absolute eosinophil count more than 10,000/cu.mm) despite adequate therapy. Skin biopsy was suggestive of heavy fungal infection.

Results

Exome sequencing revealed a heterozygous missense variant in exon 14 of the DOCK8 gene (chr9:g.340265CG; Depth: 159x) leading to the amino acid substitution of Glutamine for Histidine at codon 541 (p.His541Gln; ENST00000432829.7) was detected. Another heterozygous missense variant in exon 44 of the DOCK8 gene (chr9:g.446515TA; Depth: 155x) resulting in the amino acid substitution of Glutamine for Leucine at codon 1909 (p.Leu1909Gln; ENST00000432829.7) was detected.

The child responded after systemic antifungals and topical application of potassium iodide solution.

Conclusion

Hyper-IgE recurrent infection syndrome 2 (HIES2) (OMIM#243700) is caused by homozygous or compound heterozygous mutations in the DOCK8 gene. Having a high index of suspicion in children with atypical/recurrent or non-resolving infections with detailed evaluation of basic investigations like complete blood counts and confirmation with specialized investigations helps to get a comprehensive diagnosis for the index case and also provides an opportunity to offer prenatal diagnosis in subsequent pregnancies.

P-42

Patients focused aspects in rare diseases

VARICELLA ZOSTER VIRUS (VZV) ACUTE RETINAL NECROSIS COMPLICATED BY RETINAL DETACHMENT IN A YOUNG IMMUNOCOMPETENT PATIENT: A CASE REPORT.

Imane Roufik, Yassine Elbenaissi, Youssef Sefsafi, Marcos Vieira, Khaoula Tahani, Mohammed Elqatni, Khalid Ennibi

Center for Virology, Infectious and Tropical Diseases, Mohammed V Military Training Hospital, Morocco

Acute retinal necrosis (ARN), also known as "herpetic retinal necrosis", is a viral disease. It is rare in frequency, but serious, compromising visual prognosis. The infecting agent is a virus of the herpes group: herpes simplex (type 1 or 2), herpes zoster (shingles - chickenpox) and cytomegalovirus (CMV). A 40-year-old female patient with no previous pathological history presented with an influenza-like illness, productive cough and submaxillary adenopathy. 5 days later, she presented with a red and painful right eye, with a unilateral drop in visual acuity, initially treated as viral conjunctivitis, but with no improvement, Ophthalmological examination with fundus and retinal angiography revealed severe unilateral granulomatous panuveitis of the right eye. Anterior chamber puncture and multiplex viral PCR were consistent with positive VZV serology. Occulo-orbital MRI was normal. The diagnosis was post-VZV viral retinal necrosis of the right eye. The patient was treated with intravenous (IV) acyclovir for 5 weeks and oral corticosteroids at a dose of 1 mg/kg/day. Complicated by retinal detachment on D3 of treatment, she underwent emergency surgery. Evolution under antiviral treatment and after surgery was favorable without bilateralization. VZV is rarely responsible for necrotizing retinitis, in cases of immunocompetence and tragic progressive retinitis compromising visual prognosis. Unfortunately, some of these retinitis cases remain resistant to treatment and are still always dependent on research efforts to improve their prognosis.

P-43

Rare syndromes

A CASE OF AMYOTROPHIC-LIKE LATERAL SCLEROSIS, REVEALING VARICELLA VASCULITIS IN A PATIENT LIVING WITH HIV (PLHIV).

Imane Roufik[1], Nissrine Jait[2], Hajar Khibri[2], Mouna Maamar[2], Hicham Harmouch[2], Zoubida Tazi Mzaalak[2], Mohamed Adnaoui[2]

[1]*Center for Virology, Infectious and Tropical Diseases, Mohammed V Military Training Hospital, Morocco*
[2]*Department of Internal Medicine, Geriatrics and Clinical Hematology, Ibn Sina Teaching Hospital, Morocco*

Amyotrophic lateral sclerosis (ALS) is a rare neurological presentation complicating the evolution of an infection with the human immunodeficiency virus (HIV). The atypical clinical picture should prompt a search for unusual causes. We report the case of a 38-year-old patient with no previous pathological history, followed for one year for HIV infection with profound immunosuppression, having presented with signs of spinal cord compression. The work-up revealed periventricular nodular lesions on cerebral-medullary MRI. The patient was treated with antibacillary agents and corticosteroids without improvement, and neurological signs worsened. Clinical examination revealed a quadripyramidal syndrome, hypotrophy of the thenar and hypothenar lodges and discrete fasciculations. Cerebral-medullary MRI revealed extensive pyramidal bundle involvement and cerebral-medullary vasculitis lesions with grafting, most likely infectious. VZV PCR was positive in the CSF. Fundus examination showed infectious retinitis with anterior uveitis of the right and left eyes. Under antiviral and antitoxoplasmic treatment, the evolution was spectacular. The diagnosis of ALS like on varicella cerebral vasculitis in a PLHIV was retained. Given the ineffectiveness of neuroprotective approaches in the treatment of classic ALS targeting retroviral elements could represent a new therapeutic approach. Indeed, in some patients with ALS-Like syndrome, treatment with ARVs has resolved neurological symptoms and improve vital prognosis, suggesting that stabilization or in ALS-Classic patients may not be an unrealistic goal.

P-44

Patients focused aspects in rare diseases

NOSOCOMIAL POST-RASCHIANESTHESIA MENINGITIS, WITH ACINETOBACTER BAUMANNII AND ESCHERICHIA COLI COMPLICATING A CAESAREAN SECTION, IN A YOUNG IMMUNOCOMPETENT PATIENT; A CASE REPORT

Imane Roufik[1,2], Yassine Elbenaissi[1,2], Youssef Sefsafi[1,2], Youssef Aadi[1,2], Marcos Vieira[1,2], Khaoula Tahani[1,2], Mohammed Elqatni[1,2], Khalid Ennibi[1,2]

[1]*Center for Virology, Infectious and Tropical Diseases, Mohammed V Military Training Hospital, Morocco*
[2]*Center for Virology, Infectious and Tropical Diseases, Mohammed V Military Training Hospital, Morocco*

Introduction Acinetobacter baumannii is a frequent agent of nosocomial infections, often proving to be often multi-resistant. However, it is rarely implicated in nosocomial meningitis and is exceptionally a source of postrachianesthesia meningitis which is a difficult infection to diagnose and treat. Observation We report a case of post-operative nosocomial meningitis caused by multidrug-resistant Acinetobacter baumannii in association with Escherichia coli, following a caesarean section in a young patient who had received intrathecal anesthesia. The diagnosis was made on the basis of clinical, biological and microbiological arguments. The evolution was favorable under antibiotic therapy. Discussion Nosocomial meningitis may be encountered in the aftermath of invasive neurosurgical procedures (craniotomy, internal or external ventricular drainage, etc.), or following severe head trauma. Gram-negative bacilli are often involved. Meningitis complicating epidural or spinal anesthesia are rare, involving bacterial meningitis. Acinetobacter baumannii is very rarely implicated. Conclusion Post-spinal anaesthesia meningitis is a serious complication that can be life-threatening. their diagnosis and management are difficult due to their atypical presentation. Antibiotic therapy is relatively well codified, but mainly concerns meningitis following neurosurgical intervention. Prevention involves raising awareness among young doctors of the need to the application of strict asepsis measures.

P-45

General challenges in rare disease

IMPLEMENTING COMMON DATA ELEMENTS IN RARE DISEASES: CHALLENGES AND LESSONS LEARNED FROM THE INTERNATIONAL LANDSCAPE

Noémi Dahan-Oliel[1], Shahrzad Nematollahi[1], Peter Robinson[2], Klaus Dieterich[3], Harold Van Bosse[4], Isabel Filges[5], JIP De Vries[6], Victoria Castillo Sanchez[7], Tony Pan[8], Ishaan Lodha[9], Coleman Hilton[10], Hamdy Reggie[1]

[1]*Research, Shriners Hospital for Children, McGill University, Canada*
[2]*Genomics, The Jackson Laboratory for Genomic Medicine*
[3]*Genomics, Institute of Advanced Biosciences*
[4]*Orthopedics, St. Louis University*
[5]*Genetics, University Hospital Basel*
[6]*Obstetrics Gynecology, Vrije Universiteit*
[7]*Barcelona, Patient representative*
[8]*Computer Engineering, Emory University*
[9]*School of Computer Science, Georgia Institute of Technology*
[10]*Department Data Engineering and Analytics, Shriners Hospital for Children*

Background: Arthrogryposis Multiplex Congenita (AMC) is a group of rare conditions, characterized by multiple joint contractures. Knowledge on AMC is greatly challenged by lack of unified data frameworks, inconsistent terminologies, and incompatible data management systems.

Objectives: To address the challenges by: (i) Identifying common data elements (CDEs); (ii) Standardizing the CDEs; (iii) Developing an IT infrastructure.

Methods: i) An international mixed-methods study was designed to achieve consensus among clinicians, lived-experience individuals, and researchers using focus groups and 3-rounds of online Delphi survey. ii) AMC phenotypes were standardized using Human Phenotype Ontology (HPO) database. Data curations for joint contractures were presented using multidisciplinary collaborations with clinicians, HPO developer's team, bioinformaticians, and computational biologists. iii) The federated IT structure was designed in RedCap platform based on electronic case report forms from the Shriners-AMC registry.

Results: i) Consensus was achieved for 321 data elements among 45 experts from 11 countries in North America, Europe, and Australia. ii) Standardization of sixty-five phenotypes resulted in 61% complete match and 39% incomplete/no match. Data curations developed for 27 new terms and 58 re-structure/re-annotation, resulting in statistically significant improvement in number of standardized phenotypes (P= 0.04). iii) The federated data model contains FAIRified (Findable, Accessible, Interoperable, Reusable) dataset, allowing the data repository to access, collate, and store the whole dataset in an authorized manner. Ongoing steps include calibrate local platforms for data discovery/retrieval and development of the governance structure.

Conclusion: To augment our understanding of rare diseases, multidisciplinary collaborations, especially with patients/communities, are a prerequisite to create a holistic knowledge base. Standardized datasets and consistent data frameworks are needed to efficiently tackle research challenges and leverage efforts for knowledge translation, mobilization and sustainability.

P-46

Patients focused aspects in rare diseases

MEANINGFUL ENGAGEMENT WITH PATIENTS IN A RARE DISEASES REGISTRY: PROPOSED FRAMEWORK FOR ARTHROGRYPOSIS

Julia Lampasona[1], **Noémi Dahan-Oliel**[3], Kristen Donlevie[2], Linda C. Li[4], Shahrzad Nematollahi[3]

[1]*School of Physical and Occupational Therapy, McGill University*
[2]*Occupational Therapy, Boston University*
[3]*Research, Shriners Hospital for Children, Mcgill University, Canada*
[4]*Clinical Research, University of British Columbia*

Background: Arthrogryposis Multiplex Congenita (AMC) is a group of rare conditions, characterized by multiple joint contractures. Limited knowledge on AMC has prompted expansion of the North American AMC registry to the international level. People with lived experience (PLEX) were engaged in our international efforts, yet there is a need to use and adopt an established framework for meaningful engagement for PLEX in AMC research to guide best practice.

Methods: We used the International Association for Public Participation (IAP2) Spectrum and the Patient Engagement in Research (PEIR) Framework as proof of concepts. Levels of engagement were developed by collaborations with the international AMC consortium, experts, and PLEX across North America and Europe. Modifications in the frameworks were implemented based on the PLEX feedback on the clinical and therapeutic course of AMC.

Results: Our plan for PLEX's meaningful engagement contains 25 objectives across inform, consult, involve, collaborate, and empower levels. Objectives are developed to deliver awareness, augment PLEX's feedback, develop multiway communication, co-build patient-researcher partnership, and empower PLEX.

Conclusion: Meaningful engagement of PLEX is advantageous as it ensures research is relevant, promotes collaboration and partnership, and meaningful dissemination of AMC knowledge. This new approach to AMC research is timely and can guide patient-centered care. Next steps involve application of the framework in practice and measure engagement outcomes. Our proposed framework may be applied to other rare disease research to emphasis on the importance of PLEX partnership in creation and dissemination of rare diseases knowledge.