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Abstract Book

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New treatment modalities

Zebrafish Type I Interferonopathy Models

Alicia Martínez-López[1,3], Francisco J. Martínez-Morcillo[1,2,3], Haleh Nikzamir[1,2,3], Beatriz Bernal-Bermúdez[1,2,3], Teresa Martínez-Menchón[1,3,4], Pablo Mesa del Castillo[1,3,4], María L. Cayuela[1,3,4], Victoriano Mulero[1,2,3], **Diana García-Moreno**[1,3]

[1]*Inmunidad, inflamación y cáncer, Instituto Murciano de Investigación Biosanitaria Pascual Parrilla (IMIB Pascual Parrilla), Spain*

[2]*Cell Biology and Histology, University of Murcia, Spain*

[3]*Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER), Instituto De Salud Carlos III (ISCIII), Spain*

[4]*University Hospital Virgen de la Arrixaca, Murcia, Spain*

Type I Interferonopathies are a heterogenic group of rare diseases associated with an increase of type I interferon (IFN). The main challenge for the study of Type I interferonopathies is the lack of a well-founded animal model in which better characterize the phenotype as well as to perform fast and large drug screenings to offer the best treatment options. We report the development of several zebrafish models of interferonopathy by the genetic inhibition of an array of genes involved in this disease, including *isg15*, *copa*, *usp18* and *samhd1* using the CRISPR/Cas9 technology or by the overexpression of *ifih1* mRNA carrying the human mutation p.Arg742His. The phenotype characterization is defined by the analysis of the IFN score by measuring the expression of several interferon stimulated genes (ISGs) by RT-qPCR after a suboptimal stimulation with poly I:C or type I IFN, and also by the use of different zebrafish inflammation reporters (Tg(*nfkb:GFP*), Tg(*lyz:red*), Tg(*isg15:gfp*)). As a validation of the method, drugs inhibiting the IFN cascade at different levels, including Baricitinib (Jak1/Jak2 inhibitor), Amlexanox (Tbk1 inhibitor) and H151 (Sting inhibitor) were used to counteract the induction. The results show that zebrafish overexpressing the human mutation of i*fih1* or knockout for *isg15*, *copa*, *usp18* or *samhd1* overexpressed ISGs when treated with a suboptimal concentration of poly I:C or type I IFN. Moreover, this overexpression was abrogated when the larvae were treated with Baricitinib, suggesting that the IFN activation is specific and validating the model for drug screening proposals. These results support the use of the zebrafish as a reliable model for studying Type I interferonopathies and its potential application in large drug screening studies.

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Long-Term Retrospective Analysis of the Gene Therapy Alipogene Tiparvovec (Glybera) for Lipoprotein Lipase Deficiency: What we Learned and What's Ahead

Jasmine Chebli[1], Marie-Claude Morissette[1], Danica Stanimirovic[2], Miriam Larouche[1], Diane Brisson[1], Daniel Gaudet[1]

[1]*Department of Medicine, Université de Montréal and ECOGENE-21, Canada*

[2]*Human Health Therapeutics Research Centre, National Research Council Canada, Canada*

Background: In 2012, alipogene tiparvovec (AAV1-LPLS447X, Glybera®) was the first gene replacement therapy to be approved in the occidental world. Glybera targets lipoprotein lipase deficiency (LPLD), a rare genetic disease. LPLD is associated with severe hypertriglyceridemia and risk of acute pancreatitis. Glybera has been withdrawn from the market for cost issues. Long term data on Glybera efficacy and tolerability are crucial for the development of next generation gene therapies for LPLD and other rare diseases.

Objective: This 10-year follow-up retrospective study analysed the risk of morbidity associated with a single dose of Glybera.

Methods: Nineteen LPLD patients were treated with a single treatment of Glybera. Clinical markers of efficacy and occurrence of clinical events were followed long-term (10 years) and categorized as definite or probable pancreatitis or acute abdominal pain events.

Results: After 6 years of treatment, Glybera was associated with a lower frequency of pancreatitis events and an overall reduction in health care resource use. 44.4% of patients who participated in a chylomicron kinetics study (4/9) still presented signs of improvement after 6 years. There was no relationship between the incidence of events and the number of LPL gene copies injected or the administration of immunosuppressive regimen. There was no residual clinical benefit observed after 10 years.

Conclusion: Lessons learned from the long-term follow-up of patients treated with Glybera suggest that its efficacy is limited over time and illustrate the need of developing potent and affordable next generation gene therapies for rare diseases such as LPLD, what is currently underway.

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New treatment modalities

TrxR Inhibitor Auranofin, as a Potential Treatment of Angiomyolipoma and Lymphangioleiomyomatosis?

Judit Bóvári-Biri[1,2], ElHusseiny Mohamed Mahmoud Abdelwahab[1,2], Vera Krymskaya[3], Ryan Rue[3], Jillian Evans[3], Judit Erzsébet Pongracz[1,2]

[1]*Department of Pharmaceutical Biotechnology, University of Pécs, Hungary*

[2]*Szentagothai Research Centre, University of Pécs, Hungary*

[3]*Department of Medicine, Pulmonary, Allergy and Critical Care Division, University of Pennsylvania, Perelman School of Medicine, USA*

Background: Angiomyolipoma (AML) and lymphangioleiomyomatosis (LAM) are rare diseases characterized by mutations in tuberous sclerosis (TSC) genes. The mutation of TSC1 or 2 genes induces an enhanced activation of the mammalian target of rapamycin pathway (mTOR) leading to intense proliferation. mTOR inhibitor, rapamycin is approved for the treatment of LAM and AML, however, in some patients, the adverse effects can force discontinuation of the treatment. As no other drugs are available to replace rapamycin, deterioration of the patient's condition can ensue.

Objectives: Our previous studies showed that mitochondrial function is also affected by TSC mutation. In the present study, we aimed to target mitochondria in TSC mutant cells and identify a potential new drug combination,that results in both reduced proliferation and induction of apoptosis.

Methods: AML and LAM cell lines were treated with rapamycin and auranofin either alone or in combination. To determine the effects and mechanism of action of mono- and combined drug treatments on TSC mutant and TSC wild-type control cells, cell proliferation assay, mitochondrial staining, electron microscopy, Western blot, Cell Stress Protein Array, and enzyme activity assays (TrxR, Caspase) were performed.

Results: The study revealed that the inhibition of proliferation and the induction of apoptosis are more effective in the case of auranofin and rapamycin combination treatment, than mono-treatment by either drug.

Conclusions: as TrxR activity is an important regulator of diseases triggered by TSC mutations, combination of the two clinically approved drugs rapamycin and auranofin could improve efficacy of therapy.

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New treatment modalities

Novel siRNA-based Therapeutic Approach for Megacystis Microcolon Intestinal Hypoperistalsis Syndrome (MMIHS)

Riccardo Ottalevi[2], Isabella Baldini[1], Antonio Infascelli[1], Antonio PM Graziani[1], Greta Valoti[1], Noemi Sabatini[1], Maria Chiara Masciovecchio[1], Chiara Ciace[1], Davide Clementoni[1], Anna Lo Iacono[1], Gianluca Iodice[1], Juan Caceres[2], Michela Luciano[1], Riccardo Paone[1]

[1]*Research & Development, Dante Labs, Italy*

[2]*Research & Development - Software and Bioinformatics, Dante Labs, Italy*

Background MMIHS is a rare form of functional intestinal obstruction in the newborn. Mutations in the *ACTG2* gene, leading to disruption of γ-2 enteric actin filaments and impaired contraction of intestinal smooth muscle cells, have been linked to MMIHS in multiple studies. Even though survival has improved in recent years, MMIHS is a condition that requires invasive palliative treatments.

Objectives To meet the need for novel therapeutic approaches for MMIHS, we designed a group of therapeutic siRNA to specifically target the *ACTG2* mutant allele.

Methods WGS was performed on DNA isolated from chorionic tissue of a 13th week pregnant patient presenting an echography with alteration of gut and bladder of the newborn. EXTENSA™ software has been used to identify the pathogenic *ACTG2* variant (NP_001606.1:p.Arg178Cys) and a Machine Learning (ML) software has been used as prediction tool for the identification of 8 siRNAs with the most discriminatory power between $ACTG2^{mutant}$ and $ACTG2^{WT}$ mRNA. *In vitro* preclinical studies have been performed on HEK293 cells to evaluate the silencing of the $ACTG2^{mutant}$ mRNA highly specific manner.

Results Preliminary data suggest that our selected siRNA specifically target the $ACTG2^{mutant}$ mRNA and reduce the expression of mutant γ-2 enteric actin while showing no effect on $ACTG2^{WT}$, thus enabling a condition of haplosufficiency.

Conclusion Our study proposes a therapeutic approach based on siRNA as a novel treatment for MMIHS, identified siRNA sequences as good candidates for the development of a new drug and underscore a translational impact for future strategy to cure this disease.

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New treatment modalities

Evaluating Protective and Regenerative Ability of a Phyto Compound against Rotenone Induced Neuro Toxicity in SH-SY5Y Cell Line Model of Parkinson's Disease

Mohamed Arif[1], Dr. Radhika Raveendran[2], Dr. Mukesh Doble[2,3]
[1]*R&D, Phyto Specialities Pvt. Ltd., India*
[2]*Department of Biotechnology, Indian Institute of Technology Madras (IITM), India*
[3]*Department of Biotechnology, Indian Institute of Technology Madras (IITM), India*

Background: Parkinson's Disease is characterized by mitochondrial dysfunction, impaired energy metabolism and dysfunctional autophagy resulting in Alpha Synuclein accumulation. SH-SY5Y cells is an established model for P.D and Rotenone is a known Mitochondrial toxin used for P.D. studies.

Objective: To evaluate the neuroprotective effect of Phyto compound PHY-001 against rotenone induced neurotoxicity by improving glycolysis and preventing mitochondrial dysfunction in comparison to Terazosin and to evaluate its neuro regenerative potential.

Methods: SH-SY5Y cells differentiated with retinoic acid were treated with rotenone. These cells were pre-treated with PHY-001 and Terazosin at different concentrations and their levels of Pyruvate, ATP, MMP were compared and Cell viability studied.

Results: Pyruvate level in rotenone group was 6% compared to control at 91.2%; Terazosin at 64% and PHY- 001 at 65%. ATP levels of rotenone group was 8.25% compared to control at 87.5%, Terazosin at 47% and PHY-001 at 50%. MMP was significantly reduced in rotenone group while Terazosin and PHY-001 restored normal levels. MTT Assay has produced maximum cell viability of 95.5% recovery with PHY-001 with 100 µ g/mL in 24h. This was substantiated by fluorescence and imaging study.

Conclusion: As confirmed by this study PHY-001 could protect neurons against rotenone induced toxicity. As many factors link Parkinson's Disease and Gaucher Disease like, Mitochondrial dysfunction, decrease in LAMP1, LAMP2 and TFEB leading to lysosomal dysfunction and autophagy resulting in accumulation of substrates-Alpha synuclein and Sphingomyelin, we suggest that PHY-001's therapeutic benefits in treating Storage Disorders like Gaucher and Fabry diseases can be explored.

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Case Report: Anesthesia Management for Hysterotomy in a Case of Morquio`s Syndrome

Payman Yazdkhasti[4], Fariba Almassi[1], Pupak Rahimzadeh[3,5], Sara Asadollah[2], Payman Yazdkhasti[4]

[1]*Obstetrics and gynecology, assistant professor, Iran University of Medical sciences,, Iran*

[2]*Obstetrics and Gynecology, Iran-Tehran University of Medical sciences, Iran*

[3]*Anesthesia and Pain management, Iran -Tehran university of Medical sciences, Iran*

[4]*Anesthesia and Pain Managment. Anesthesiologist, Tehran Iran University of Medical Sceinces, Iran*

[5]*Anesthesia and pain Management. Assistant of Professor, Tehran Iran University of Medical Sciences, Iran*

Abstract:

**Morquio`s syndrome** is an autosomal recessive disease. It is from mucopolysacaridosis group disease and it`s obvious clinical signs are severe skeletal dysplasia and normal intelligence.

Deposition of keratan sulfate in different tissues is seen and with progression of the disease, connective tissue of cornea, airways, lung and heart valves will be involved.

In this article we present a case of Morquio`s rare syndrome that we terminated the pregnancy due to severe respiratory distress of mother and also we present the anesthesia management of this case.

Keywords: Anesthesia, pregnancy, Morquio syndrome

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New treatment modalities

Safety and Efficacy of Intravenous Immunoglobulin (IVIG) Treatment in Patients with Neuropathic Corneal Pain

Pedram Hamrah[1], Betul Bayraktutar[1], Oscar Soto[1], Ann Louise Oaklander[2], Khosro Farhad[2]

[1]*Ophthalmology, Tufts Medical Center, Tufts University School of Medicine, USA*
[2]*Neurology, Massachusetts General Hospital, USA*

Background: Neuropathic corneal pain is a rare disease caused by a lesion/injury to somatosensorial nerves nervous system. No FDA approved treatments are available and many cases are refractory to therapy.
Objective: Intravenous immunoglobulin (IVIG) have been reported to be an efficient treatment alternative in immune-mediated small fiber neuropathy patients. Therefore, we aimed to evaluate the efficacy of IVIG treatment in patients with NCP.
Methods: Medical records of patients who were diagnosed with NCP and small fiber neuropathy based on clinical, in vivo corneal confocal microscopic, and positive skin biopsy findings, and were initiated with IVIG treatment were evaluated retrospectively. Demographic features of patients, corneal fluorescein staining (CFS) scores (Oxford scale), and symptoms questionnaires were reviewed at baseline and 6-months treatment follow-up.
Results: Fourteen NCP patients who were refractory to topical and systemic therapies were included. The mean age of patients was 43.2±13.3 years. Twelve patients had at least one positive auto-/dysimmune Ab on serology. Four patients discontinued treatment due to side effects. In the remaining patients, mean pain intensity score (scale 0-10) in last 24 hours and in last 2 weeks improved from 5.4±0.8 to 3.6±0.9 ($p=0.004$) and from 5.0±0.9 to 3.7±0.9 ($p=0.02$), respectively. The impact of pain on quality of life reduced significantly in the follow-up visit ($p=0.03$). Patients reported a mean of 32.5% eye pain relief compared to their baseline visit.
Conclusion:
IVIG treatment provides significant pain relief and improves quality of life in NCP patients. Therefore, in selected cases, IVIG treatment seems to be promising in NCP management, when refractory to other therapies.

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Patients focused aspects in rare diseases

Next Generation Sequencing in Patients with Idiopathic Erythrocytosis

Andrea Benetti[1], Irene Bertozzi[1], Giulio Ceolotto[2], Giacomo Biagetti[1], Maria Luigia Randi[1]
[1]*Department of Medicine – DIMED, University of Padua, First Medical Clinic, Italy*
[2]*Department of Medicine – DIMED, University of Padua, Emergency Medicine, Italy*

Background: In 70% of patients, the cause of their absolute erythrocytosis is not identified and a diagnosis of Idiopathic Erythrocytosis (IE) is ruled out. Erythropoietin receptor (*EPO-R*) and oxygen sensing pathway genes (*EGLN1*, *VHL*, *EPAS1*) are known causes of hereditary erythrocytosis and germinal *JAK2* alterations and iron metabolism genes (*HFE*) are found to be altered in some IE.

Methods: We searched variations of *EGLN1*, *EPO-R*, *FTL*, *FTH*, *JAK2*, *HFE*, *HFE2*, *TFR2*, *HAMP*, *SLC40A1*, *SLC11A2*, *VHL*, *BPMG*, *EPAS1* genes using an ad-hoc Next Generation Sequencing (NGS) panel in 118 sporadic IE patients (M/F =101/17; mean age 53.7±17.2 years). The patients' median haemoglobin (Hb) was 172 g/L (range 142-206) and haematocrit (HT) 51% (range 45.7-57.2). We used bioinformatics tools to analyse data and Sanger Sequencing to validate the variations observed.

Results: Gene alterations were observed in 78 (66%) patients: *HFE* variations was found in 51 cases, *EGLN1* in 18 and *EPAS1*, *EPO-R*, *JAK2* and *TFR2* in 6, 8, 9 and 11 patients respectively. Twenty-three patients (19.45%) had multiple genes putative pathogenetic variants.

Conclusions: The use of NGS ad-hoc panel opens new perspectives in the knowledge of idiopathic erythrocytosis. Genetic variants in genes yet known to cause hereditary erythrocytosis have been found in 2/3 of IE patients suggesting that these variants have to be searched also in sporadic cases. Unexpected multiple variations found in some IE cases suggests that erythrocytosis may be of multigenic nature.

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Patients focused aspects in rare diseases

An Ultra-Special Family with an Ultra-Rare Condition: Three Children with Mithcondrial Complex III Deficiency Due toHomozygous Mutations in Lyrm7

Francesca Manzoni[1], Michela Salandin[1], Elisa Boni[1], Elena Pavlidis[1], Serena Pellegrin[1], Lucio Parmeggiani[1]

Hospital of Bolzano Bozen Italy., Child Neurology and Neurorehabilitation Unit, Department of Pediatrics Central Teaching Hospital of Bolzano, Bozen, Italy

We present a family with three children affected by an ultra-rare mitochondrial disease due to a mutation in the LYRM7 gene.
The purpose of the presentation is to illustrate the clinical phenotype of this family and to emphasize that the brain MRI is a sensitive tool to diagnose leukoencephalopathies, in particular for mitochondrial leukoencephalopathies. Consistent patterns of abnormalities could be linked to specific mitochondrial dysfunctions and gene defects, guiding the diagnosis of an increasing number of diseases.

The radiological phenotype associated with mutations in LYRM7 is distinctive: multifocal white matter abnormalities in the periventricular and deep cerebral white matter with cavitations. Small concentrations of Pyocyanin are a promising therapeutic strategy against CIII disorders, such as mitochondrial disease due to a mutation in the LYRM7 gene.

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Patients focused aspects in rare diseases

Patients' and Caregivers' Understanding of Classical Homocystinuria in Brazil

Andrei Meurer de Andrade[1,2], Ana Paula Pedroso Junges[1,2], Simone Arede[3], Soraia Poloni[1,4], **Ida Vanessa Doederlein Schwartz**[1,2,5]

[1]*Avaliação de Tecnologias de Saúde em Genética Médica, Hospital de Clínicas de Porto Alegre, Brazil*

[2]*Faculdade de Medicina, Universidade Federal do Rio Grande do Sul, Brazil*

[3]*Coordinator, Associação Mães Metabólicas, Brazil*

[4]*Serviço de Nutrição, Hospital de Clínicas de Porto Alegre, Brazil*

[5]*Serviço de Genética Médica, Hospital de Clínicas de Porto Alegre, Brazil*

Background: Classical homocystinuria (HCU) is an inborn error of metabolism caused by deficient activity of cystathionine β-synthase. In Brazil, HCU is not included in its newborn screening program. Previous data by our group shows that most Brazilian patients with HCU are late-diagnosed, non-responsive to B6 and non-adherent to treatment.

Objectives: To assess patients` and caregivers` understanding about HCU.

Methods: An online questionnaire composed of ten questions was developed by our team and a representative of patients/caregivers, then distributed in the midia from July to August 2022. A-hundred participants (24 patients and 76 caregivers) answered the questionnaire.

Results: Out of 100 replies, 42 were given by patient`s mothers, 24 by patients themselves, 20 by fathers and 14 by brothers/sisters. Replies referred to a total of 59 patients (mean age of 21.9 years). Only 29 of responders understand the biochemical basis for HCU and 37 (37%), its recurrence risk. Regarding symptoms and treatment, 18 (18%) understand which complications HCU can cause and 20 (20%) know the main forms of treatment. The main treatments reported were folic acid (85%) and pyridoxine (80%) supplementation. Out of five options, 90 (90%) were able to identify the food with the highest protein content and 66 (66%), the food with the smallest protein content.

Conclusion: Our findings reflect the vulnerability of people with HCU, as the understanding of HCU causes, treatment and management is still low among patients and caregivers. This is probably contributing to the low adherence to treatment.

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Precision Medicine through NGS in a Reference Center for Rare Diseases: The Case of the National Institute Fernandes Figueira (FIOCRUZ) in the State of Rio de Janeiro, Brazil

Juan Llerena Junior[1], Natana Rabelo[2], Maria Eduarda Gomes[2], Isabelle Moraes[2], Sayonara Gonzalez[2]

[1]*Medical Genetic Center, Instituto Nacional Fernandes Figueira - Fiocruz, Brazil*

[2]*Genomic Medicine Laboratory, Instituto Nacional Fernandes Figueira - Fiocruz, Brazil*

BACKGROUND: The Rare Disease Reference Center in the state of Rio de Janeiro, Brazil.

OBJECTIVE: Reporting 285 molecular investigation for atypical clinical presentations, rare syndromes and/or nosological groups with clinical/genetic heterogeneity.

METHODS: Patients were investigated through Sanger gene targeted and/or customized gene panel (6,700 genes) Trusight One Expanded (Illumina) methods.

RESULTS: Overall 270 patients received a definitive diagnosis. Clinical-molecular experiences exceeded our expectations exploring different scenarios: (1) rare syndromes - Salla disease(SLC17A5), Fuhrmann/Al-Awadi/Raas-Rothschild/Schinzel syndrome(WNT7A), glomuvenous disease(GLMN), Ullrich muscular dystrophy(COL6A3), Cantú syndrome(ABCC9), AR degenerative vitreoretinopathy(LRP5), muscular dystrophy dystroglycanopathy type C(FKTN), leukodystrophy with calcifications and multiple strokes(COL4A1), among others; (2) change in clinical management - suspected xeroderma pigmentosum that resulted in a syndrome with low tumor probability despite increased UV sensitivity (OMIM 614640)(UVSSA); (3) within the rasopathies: diagnostic switch - Noonan to Coffin-Siris (ARID1B); identification of a new variant(LZTR1); and, a case of double dominant heterozygote(PTPN11; NF1); (4) to propose atypical mechanisms of inheritance - digenic inheritance in a familial Ellis Van Creveld phenotype in three siblings (DYNC2H1;C21orf2); McKusick syndrome with glaucoma carrying a double recessive mutations (RMRP;CYP1B1); (5) gene reversion by somatic recombination in Fanconi anemia (Groups A,F and L); (6) solving technical problems in Sanger due to inadequate annealing of primers due to polymorphism (Tanatophoric I and Glomuvenous Disease); and, (7) different DNA tissue sources - from lung biopsy maintained in liquid nitrogen (alveolar capillary dysplasia negative for FOXF1, FOXC2 and FOXL1).

CONCLUSION: The workflow dynamics among the clinical and genomic teams were essential at all stages for reaching a diagnostic precision.

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Patients focused aspects in rare diseases

Case Report on Early Diagnosis of Abetalipoproteinemia

Julio Flores[1], **Carlos-Patricio Acosta-Rodríguez-Bueno**[1], Magdalena Cerón-Contreras[1], Alejandra Reyes-De la Rosa[1], Pamela Palacios-Vega[1], Ana Torres-Fraga[1]
Pediatric Internal Medicine, Hospital Infantil De México "Federico Gómez", Mexico

Abetalipoproteinemia is a rare recessive autosomal disorder that involves mutation on the microsomal triglyceride transfer protein (MTTP) gene. Its prevalence worldwide is reported on 1: 1 000 000. We present an 11 months old infant diagnosed at the Hospital Infantil de Mexico Federico Gomez, who came with failure to thrive, lipid malabsorption. On blood smear we found acanthocytosis, on hepatic ultrasound we found hepatic steatosis. An endoscopy was performed where an image was found in snowflakes and in the histopathology lipid deposits in the enterocytes. We found two pathogenic variants identified in MTTP gene with partial deletion in exons 11-16 and c.552 duplication. The patient was treated differently from what is currently described, obtaining positive results, such as improvement in neurodevelopment according to age. Our objective is to describe this rare disease as well as the established management.

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Patients focused aspects in rare diseases

The Impact of Neuropathic Corneal Pain on Quality-of-Life Dimensions with Regards to Age and Gender

Leyla Mirzaee, Akhil Mekka, Maria J. Lopez, Navneet Ramesh, Bijan Khaksari, Gabriela Dieckmann, Dilruba Koseoglu, Arsia Jamali, Pedram Hamrah

Tufts Medical Center, USA

Background:
Neuropathic Corneal Pain (NCP) is a rare disease that is caused by a primary lesion or dysfunction of the ocular nervous system. The impact of NCP on patients' quality of life (QoL) dimensions has not been studied to date.

Objective:
To measure the impact of NCP on QoL dimensions.

Methods:
A cross-sectional, retrospective, comparative study, including 119 patients was conducted. Demographics, ocular pain assessment survey (OPAS), ocular surface disease index (OSDI) scores, and correlation of ocular discomfort to physical (vision-related), social and psychological dimensions of QoL assessed. The impact of age and sex on pain and interference on QoL was evaluated.

Results:
Mean age of the cohort was 56.2±16.0 years. Mean pain intensity scores (scale 0-10) were 5.03±3.22 for last 24 hours and 4.77±3.51 for last 2 weeks. The interference of pain on physical (visual-related) QoL dimension (0-10 scale) was reading/computer (5.54±3.46), driving/TV (4.59±3.32), and general activity (3.87±3.04); mood (5.66±3.48) and sleep (3.46±3.18) for psychological; enjoying life/social relations (5.15±3.50) for social dimension of QoL. Pain had significant impact on the vision-related dimension of QoL (r 0.025; p 0.05), but not on general activity (r= 0.04 p= 0.73). Mood was highly impaired (r= 0.43 p= 0.0003), and enjoying life/social relations were impaired by pain (r= 0.24 p= 0.04). Age and sex did not demonstrate any significant impact on QoL (p 0.05).

Conclusion:
NCP causes ocular discomfort and pain, which evokes a pronounced interference with physical (particularly vision-related), psychological, and social dimensions of QoL, regardless of age and sex.

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Patients focused aspects in rare diseases

Clinical Usefullness of Inhibin B in Patients with Granulosa Cell Tumors Based on the Observation of Patients Treated at the Oncology Center in 1998-2018

Magdalena Kowalska, Piotr Sobiczewski, Beata Kotowicz, Mariusz Bidziński
Gynecology Oncology, National Oncology Center, Poland

Granulosa cell tumors are rare ovarian tumors characterized by slow development, early advancement at diagnosis, hormonal activity and possibility of relapse even after many years.

Analysis included 139 patients - 25 patients with recurrence and 114 patients without. Measurements were collected in the range of 18-12, 12-6, 6-0, 0-6, 6-12, 12-18 months in patients with relapse and 6 consecutive measurements after surgery in patients without.

The aim of the study:

· Find clinical usefulness of inhibin B in detecting disease recurrence

· Find the relationship between inhibin B and clinical and pathological features in patients with granulosa cell tumors.

· Assess inhibin B as a marker supporting imaging methods in detecting late relapses

· Assesse the predictive value of inhibin B for the recurrence and the prognostic value of inhibin B for death

Inhibin B concentration was found to be the most predictive of recurrence in the 6-0 months. The concentration of inhibin B is an independent predictor of recurrence. There was a strong trend towards an independent prognostic factor for death in the range of 6-0 months before recurrence. Inhibin B was the most predictive of recurrence and death compared to other clinical parameters (FIGO stage, presence of ascites and tumor diameter). The cut-off point for the risk of recurrence was at 25 pg / ml and above 132 pg / ml was associated with worse prognosis.

Inhibin B is a sensitive and specific predictor of recurrence and useful tool supporting the decision to perform an imaging examination despite the absence of symptoms.

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Patients focused aspects in rare diseases

Fabry Disease and Systemic Sclerosis: a Maleficent Pair

Malika Boucelma, Hind Arzour, Farid Haddoum
University of Algiers, Algeria

Fabry disease is a X-linked lysosomal storage disorder caused by mutations in the GLA gene producing α-Galactosidase A enzyme (α-Gal A) deficiency. Systemic sclerosis (SSc) is a rare immune-mediated vasculopathy characterized by fibrosis of the skin and internal organs. The coexistence of these two entities remains exceptional. We describe a case of 54 years old women with cardiac variant of Fabry disease, a diagnosis based on the presence of Hypertrophic cardiomyopathy complicated by atrial fibrillation. The diagnosis was confirmed by a low alpha galactosidase enzyme activity and identification of GLA gene mutation. On follow up, she developed sclerodactily, Raynaud phenomenon, digital ulcers, microvascular involvement and positive centromere antibodies. The particularity of this case is the coexistence of two orphan disease which require a review of the literature.

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Patients focused aspects in rare diseases

Psychological Distress of Adult Patients Consulting a Center for Rare and Undiagnosed Diseases: a Cross-Sectional Study

Meike Mund[1], Natalie Uhlenbusch[2], Franziska Rillig[1], Christina Weiler-Normann[1,3], Theresia Herget[4], Christian Kubisch[1,4], Bernd Löwe[2], Christoph Schramm[1,3]

[1]*Martin Zeitz Center for Rare Diseases, University Medical Center Hamburg-Eppendorf, Germany*

[2]*Department of Psychosomatic Medicine and Psychotherapy, University Medical Center Hamburg-Eppendorf, Germany*

[3]*I. Department of Internal Medicine, University Medical Center Hamburg-Eppendorf, Germany*

[4]*Institute of Human Genetics, University Medical Center Hamburg-Eppendorf, Germany*

Background: Centers for rare diseases serve as contact points for patients with complex, often undiagnosed complaints and persistent somatic symptoms of heterogeneous origin. Little is known about psychological distress of patients consulting these centers.

Objectives: To better understand psychological distress of adult patients presenting at a center for rare diseases by determining the proportion of patients screening positive for depressive, anxiety, and somatic symptom disorders (SSD) and to identify factors associated with increased psychopathology.

Methods: Cross-sectional data from the routine care registry of the Martin Zeitz Center for Rare Diseases (MZCSE) at the University Medical Center Hamburg-Eppendorf in Germany was retrieved and analyzed. We included all adult patients presenting between October 01, 2020 and September 30, 2021, who gave written informed consent. Data obtained comprised sociodemographic variables, medical history and healthcare utilization. Well validated measures were used to screen for a depressive disorder (PHQ-8), an anxiety disorder (GAD-7), and SSD (PHQ-15, SSD-12).

Results: N=167 patients were included (age 44.5±14.3 years, 64.7% female). A total of 40.7% of the patients screened positive for a depressive disorder (PHQ-8≥10), 27.5% for an anxiety disorder (GAD-7≥10) and 45% screened positive for SSD (PHQ-15≥9 & SSD-12≥23). Factors associated with increased psychopathology included the number of symptoms, the number of different specialties consulted before and past psychotherapy.

Conclusions: Patients presenting at centers for rare diseases are likely to experience high rates of psychological distress. Systematically screening patients with rare and undiagnosed diseases for mental disorders can help to detect those at risk at an early stage and initiate adequate psychological care.

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Building a Collaborative Network for Greater Access to Innovations for Rare Lipid Diseases: The Model of the Smash Program

Miriam Larouche[1], Marcello Arca[2], Philippe Moulin[3], Jean Bergeron[4], Sophie Bernard[5], Diane Brisson[1], Eric Bruckert[6], Laura D'Erasmo[2], Alessia Di Costanzo[2], Antonio Gallo[6], Frederick Raal[7], Daniel Gaudet[1]

[1]*MEDICINE, Université De Montréal and Ecogene-21, Canada*
[2]*Medicine, Sapienza Università, Italy*
[3]*Medicine, Université Claude Bernard, France*
[4]*Biochimie, Université Laval, Canada*
[5]*Medicine, Institut De Recherche Clinique De Montréal Et Université De Montréal, Canada*
[6]*Endocrinology-Metabolism, Hôpital de la Pitié-Salpétrière, France*
[7]*Health Sciences, University of Witwatersrand, South Africa*

Background

Rare diseases are often ignored, and patients have little access to effective treatments. Once marketed, novel therapies developed through clinical trials are often expensive and their use is limited by payers claiming lack of sufficient data on the natural history of the disease and of benefit from these novel therapies. As rare diseases involve small numbers, it makes it difficult to generate trial evidence. It is therefore necessary to make use of a collective effort to document the clinical expression of rare diseases and to ensure access to effective, safe, and affordable therapies.

Objective

To build a collaborative network grouping stakeholders involved in the management of patients with rare lipid diseases with the aim of documenting the natural history of the diseases and ensuring access to affordable therapies.

Methods

The SMASH program (System and Molecular Approaches of Severe Hyperlipidemias) is creating an international network of top-level researchers, clinicians, patient organizations and stakeholders. The SMASH network provides larger sample sizes allowing a better comprehension of rare dyslipidemias and the response and impact of emerging therapies. Natural history of rare dyslipidemias will be documented through a systems approach. SMASH is using chylomicronemia and homozygous familial hypercholesterolemia as proof-of concept.

Expected Results

The SMASH network will improve the understanding of the issues, causes and consequences of rare dyslipidemias and favor and promote access to personalized treatments for patients.

Conclusion

A collaborative network is mandatory to document rare dyslipidemias and provide patient access to emerging treatments in both developed countries and emerging economies.

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Patients focused aspects in rare diseases

First Seroprevalence Study of Tick-Borne Encephalitis Virus in Healthy Agricultural Population on Jeju Island, South Korea, 2015-2018

Misun Kim[1,2] ,Sang Taek Heo[1,2], Hyunjoo Oh[1], Jeong Rae Yoo[1,2]
[1]*Internal Medicine, Jeju National University Hospital, South Korea*
[2]*Internal Medicine, Jeju National University, College of Medicine and Graduate School of Medicine, South Korea*

Background: Tick-borne encephalitis (TBE) is caused by tick-borne encephalitis virus (TBEV), of the family Flaviviridae in endemic areas in Europe and Northeast Asia. In Far East Asia, human cases of TBE have been reported in China, North Korea, and Japan, but not from South Korea.

Objectives: In this study, we investigated the seroprevalence of TBEV in an agricultural population on Jeju Island in South Korea, an area where tick-borne disease is common.

Methods: A serosurvey was carried out to determine the seroprevalence of TBEV in the agricultural population of ten rural villages of Jeju Island in South Korea between January 2015 and December 2018. The serum samples were tested for TBEV IgM and IgG using a commercial enzyme-linked immunosorbent assay (ELISA) test kit (GenWay Biotec, San Diego, CA, USA).

Results: Of the 321 serum samples collected, eight were excluded because the amount of sample was insufficient, and 313 samples were tested for TBEV antibodies. The mean age of the participants was 60.1±10.5 years, and 67.4% were male. A survey on Jeju Island revealed a seroprevalence of TBEV IgM and IgG of 1.3% and 0.63%, respectively.

Conclusion: The serosurvey revealed a 1.9 % TBEV seroprevalence in a farming population within South Korea. Even though the seroprevalence in the study population was lower than that reported in countries in Far-East Asia, the results confirm the possibility of TBE among people in South Korea who have contact with ticks.

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Patients focused aspects in rare diseases

Patient Oriented Research in Arthrogryposis Multiplex Congenita: From Inception to Knowledge Translation

Noémi Dahan-Oliel[1,4], Shahrzad Nematollahi[1,4], Sarah Cachecho[1], Rose Elekanachi[1,4], Doaa Taqi[1,4], Caroline Elfassy[1,4], Frank Rauch[3,4], Sena Tavukcu[1], Reggie Hamdy[2,4]
[1]*Research, Shriners Hospital for Children, Canada*
[2]*Orthopedics, Shriners Hospital for Children*
[3]*Molecular Laboratories, Shriners Hospital for Children*
[4]*Faculty of Medicine and Allied Health, McGill University, Canada*

Arthrogryposis multiplex congenita (AMC) refers to the development of multiple congenital contractures in which affected joints become permanently fixed in a flexed or extended position, and occurs in 1 in 3000 live births. The primary underlying cause of AMC is suspected to be decreased fetal movement during development (i.e., fetal akinesia), attributed to genetic and/or environmental factors. Next generation sequencing has been shown to be useful in delineating novel gene mutations and phenotype-genotype correlation enabling the investigation of known and novel disease genes. Early detection, evidence-based treatments and health services optimized to the needs of users and their families is crucial for individuals with rare diseases, such as AMC. A research program seeks to address these issues, and aligns itself with the Quebec Ministry's 2022 policy on rare diseases and provincial commitment to these individuals by advocating for patient- and family-centered approaches, health equity, and promotion of research, innovation, and collection of outcomes. Objectives. The overarching goal to improve the clinical outcomes of children with AMC by advancing research using a collaborative approach is addressed through six research projects: Project 1. Expand a registry for AMC across eight hospital sites in North America and Mexico to systematically phenotype and genotype participants. Implementing the current registry across additional sites in 500 children with AMC aims to identify outcomes post-surgery, develop a functional classification for AMC, and identify new genetic causes in AMC using cutting-edge analytical approaches of whole genome sequencing data. Project 2: Identify common data elements using a mixed-methods approach and mapping to the Human Phenotype Ontology to develop an international registry for AMC. Project 3. Creation and implementation of expert-based rehabilitation guidelines to promote a standardized approach; Project 4. Development of a disease-specific outcome measure to evaluate the impact of upper extremity joint limitations on physical function; Project 5. Elucidation of the dental and maxillofacial phenotype in children and adults with AMC; Project 6. Determination of caregivers' perspectives of caring for a child with AMC related to direct, indirect and psychosocial costs. Methodology: Each study is guided by a patient-oriented paradigm while using quantitative, qualitative and mixed-methods approaches. Significance: By engaging youth with AMC, families, and clinicians in research, we can catalyze on the expertise and lived experience to collect data on larger samples and yield more impactful dissemination of findings in rare diseases.

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Patients focused aspects in rare diseases

IGA/IWGGD Older Generation Project – Your Support Needed

Paul Guijt[2], IGA Working group Older Generation[1]
[1]-, *International Gaucher Alliance, UK*
[2]-, *International Gaucher Alliance, Netherlands*

Background: The International Gaucher Alliance (IGA) is the umbrella organization representing 60 Gaucher patient associations from all over the world.
The IGA cares about the older generation of people living with Gaucher disease. Most of them, irrespective of their type and older than 60, acquired consequences of the disease before the new treatments or without. Physical, but presumably also e.g. social. They fall out of the picture too easily.

Objective: Have a better understanding of the clinical and non-medical needs of our older Gaucher patient community, to detect unmet needs and improve their situation where we can.

Methods: A survey towards IGA member organisations, and a second survey towards elderly individuals living with Gaucher disease. Special attention was given to their language and jargon.

Results: The survey of IGA member organisations was held and its data was processed. Our poster reports preliminary outcomes. The second survey towards individuals was sent out through SurveyMonkey and is now collecting data.

The project needs anyone's support in bringing the survey to the attention of the individuals intended. Presumably, they will have difficulties with the digital format, language, and jargon, and in answering it. The survey takers are a quite rare species, occasionally quite difficult to trace and survey, so every respondent counts.

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Patients focused aspects in rare diseases

IGA/IWGGD Home Therapy Project – an Update

Paul Guijt[1], IGA Working Group Home Therapy[2]
[1]-, *International Gaucher Alliance, Netherlands*
[2]-, *International Gaucher Alliance, UK*

Background: In many countries, especially in the western countries of the EU and North America, patients have the possibility to receive enzyme replacement therapy (ERT) at home, to the satisfaction of all involved. Nevertheless, there are still many countries where home ERT is still not available or acceptable by regulators and physicians.

Objectives: To facilitate a proper home infusion therapy provision, especially in countries where home ERT is not available. To provide guidelines and perhaps other deliverables.
We hope to provide greater clarity on the importance and benefits of home infusion therapy in an attempt to make it a standard of care.

Methods: A review of relevant literature
An exploratory survey is held under the representatives of the IGA member organizations
Later a thorough field consultation will be performed

Results: The literature review is being worked on, partly to be beneficial as an overview for the broader clinical community and partly as a starting point for guideline development.
Outcomes of the survey are being formatted into a constantly updated section of the IGA website, to reflect the global status of home therapy. They are being enriched to contribute to guideline development, also through field consultation.

The guidelines and other deliverables will be developed for and with all parties involved including clinicians, nurses, patients, pharmacists, and policymakers. We developed an overall framework to bring these documents together coherently and to structure our project.

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Patients focused aspects in rare diseases

A Case of Diaphragmatic Eventration that is Misdiagnosed as Dextrocardia

Reyhane Parvin[1], Rouholah Hakimian[2], Leila Sadat Mohamadi Jahromi[3], Armin Amirian[4], Hasan Moradian[5]

[1]*Department of Physical Medicine and Rehabilitation, M.D Physical Medicine and Rehabilitation from Shiraz University, Iran*

[2]*Department of Surgery, M.D General Surgery from Shiraz University of Medical Science, Iran*

[3]*Department of Physical Medicine and Rehabilitation, M.D Physical Medicine and Rehabilitation Shiraz University of Medical Science, Iran*

[4]*Department of Surgery, Assistant Professor of Thoracic Surgery, Shiraz University Medical Science, Iran*

[5]*Department of Animal Sciences and Genetics, P.H.D of Animal Sciences and Genetics from Shahid Bahonar University of Kerman, Iran*

Eventration of the diaphragm is an unnatural elevation of an entire diaphragm. An eventration is due to a thinned diaphragm with no central muscle. We presented a 56-year-old man with reported dextrocardia with discomfort chest and dyspnea, orthostatic hypotension and loss of appetite, and dyspnea aggravated in the supine position while it subsides in sitting. The chest x-ray showed severe left-sided diaphragmatic elevation with a huge dilated colon that has compromised the left hemithorax and caused lung collapse and mediastinal shift with a hemodynamic alteration. The ECG (positive QRS complex in the lead I, negative in aVR, while limp leads placed in the regular position) called the noted history of dextrocardia into question Furthermore. A thoracic CT scan excluded the dextrocardia and revealed the left diaphragmatic elevation with a dilated segment of colon and replacement of spleen and stomach to the subdiaphragmatic area entrance of the stomach and bowel, the left flexure of colon with a displacement of the heart to the right side of the mediastinum. Due to severe dyspnea and impaired pulmonary function test, diaphragmatic plication surgery was performed. Congenital Diaphragmatic Eventration is a rare and challenging diagnosis, and CT is essential for the diagnosis.

Keywords: diaphragmatic eventration, dextrocardia, diaphragmatic plication.

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Raising awareness for rare diseases

Coccidioidomycosis in Joint Replacement: A Review of the Literature with Case Presentations

Francesca Anna Giordani
Medicine and Surgery, University of Rome, Tor Vergata, Italy

Coccidioidomycosis is a rare fungal infection endemic to certain regions of the Americas. In rare cases, the organism may infect the musculoskeletal system resulting in a prosthetic joint infection (PJI). Due to its rarity and difficulty in diagnosis, recognition and treatment of coccidioidomycosis PJI is often delayed. Furthermore, with limited number of case reports, a standard of care in treatment has yet to be established. We present three cases of coccidioidomycosis PJI, the extensive evaluation that led to diagnosis, and the treatment provided. This report highlights the natural progression of coccidioidomycosis in a prosthetic joint, the diagnostic features including histology, the advanced imaging, and the final treatment administered.

Our cases have a minimum 6-year follow-up with the first case appearing to have cleared after a debridement and implant retention (DAIR) procedure, while the second required a two-stage revision. The third case was misdiagnosed with primary osteoarthritis, and required revision surgery. All three cases required chronic suppressive antifungal medication. These cases all emphasize the need for good history, high index of suspicion, and coordinated care with pathology, radiology, orthopaedic surgery, and infectious disease specialists.

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Raising awareness for rare diseases

Raising Rare Disease Awareness through Social Media: the Experience of Brazilian Network for Rare Diseases

Ida Vanessa Doederlein Schwartz[1,2,3], Bibiana Mello de Oliveira[1,2], Mariana Lopes dos Santos[1,2], Milena Artifon[1], Júlia Cordeiro Milke[1,2], Amanda Maria Schmidt[1,4], Victoria Machado Scheibe[1,4], Gabriella Zanin Fighera[1,4], Betania Ponce[1], Têmis Maria Félix[1,3], Rede Nacional de Doenças Raras

[1]*Rede Nacional de Doenças Raras, Rede Nacional de Doenças Raras (RARAS), Brazil*
[2]*Genetics, Universidade Federal do Rio Grande do Sul (UFRGS), Brazil*
[3]*Medical Genetics Service, Hospital de Clínicas de Porto Alegre (HCPA), Brazil*
[4]*Universidade Luterana do Brasil, Universidade Luterana do Brasil (ULBRA), Brazil*

Introduction: The Brazilian Network of Rare Diseases (RARAS) is an initiative of 37 institutions that assist individuals with Rare Diseases (RD) in Brazil, including Reference Services for Rare Diseases, Reference Services for Newborn Screening and University Hospitals distributed in all Brazilian regions. One of the main goals of this network is to raise awareness on RD for the general population.

Objectives: To describe the construction of social media on the RARAS Network and measure their impact from 2021 to 2022.

Results: The RARAS Network social media were founded on February 28, 2021, on the Rare Disease Day and obtained 2059 (Instagram®) and 1151 (Facebook®) followers. Most followers are Brazilian (98.1% and 95.8%), female (82.9% and 79.6%), 34 to 44 years old (30.3% and 20.5%), and live in São Paulo city (11.6% and 10.7%). The Facebook posts reached 32,774 users and Instagram, 14,985 users. In this period, 176 publications were made, including images and videos of awareness on RD in general; specific disorders information; scientific publications carried out by RARAS-Network and the network`s actions in the country, using lay language, in Portuguese, to broaden the understanding of the general public.

Conclusion: A wide reach of the general public was identified, demonstrating that there is an interest in this topic. There is a predominance of women among the followers, which was also observed in other studies involving the search for health-related information. It is essential to maintain and expand publicity actions in order to increase awareness on RD in the country.

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Raising awareness for rare diseases

Early Identification of Chronic Mesenteric Ischemia with Endoscopic Duplex Ultrasound

Nathkai Safi
Vascular Surgery, Oslo University Hospital, Norway

Background: Due to diagnostic delay, chronic mesenteric ischemia (CMI) is underdiagnosed. We assumed that the patients suspected of CMI of the atherosclerotic origin or median arcuate ligament syndrome (MALS) could be identified earlier with endoscopic duplex ultrasound (E-DUS).
Objectives and Methods: Fifty CMI patients with CTA-verified stenosis of either ≥50% and ≥70% of celiac artery (CA) and superior mesenteric artery (SMA) were examined with E-DUS and transabdominal duplex ultrasound (TA-DUS). Peak systolic velocities (PSV) of ≥200cm/s and ≥275cm/s for CA and SMA, respectively, were compared with CTA. Subgroup analysis was performed for the patients with (n=21) and without (n=29) prior revascularization treatment of CMI. The diagnostic ability of E-DUS and TA-DUS was tested with crosstabulation analysis. Receiver operating characteristics (ROC) curve analysis was performed, and the area under the curve (AUC) was calculated to investigate the test accuracy.
Results: In the patients with ≥70% stenosis, E-DUS had higher sensitivity than TA-DUS (91% vs 81% for CA and 100% vs 92% for SMA). AUC for SMA ≥70% in E-DUS was 0.75 and with TA-DUS 0.68. The sensitivity of E-DUS for CTA-verified stenosis ≥70% for CA was 100% in the patients without prior treatment. E-DUS demonstrated higher sensitivity than TA-DUS for both arteries with stenosis ≥50% and ≥70% in the treatment-naive patients.
Conclusion: E-DUS is equally valid as TA-DUS for the investigation of CMI patients and should be used as an initial diagnostic tool for patients suspected of CMI.

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Rare syndromes

New Genotype-Phenotype Association of FUCA2 GEN to Partial Fucosidosis Syndrome 3 Case Reports

Alzenira De Fátima Costa-Martins[1], José Luis Garcia-De-Veas[1], Laura Gort[3], Antonio Gonzalez-Meneses[2], Maria Del Amor Bueno-Delgado[2], Juan Miguel Guerrero[1,4,5], **Hada Celicia Macher**[1,4]

[1]*Clinical Biochemistry Department, Virgen Del Rocio University Hospital, Spain*
[2]*Pediatric Department, Virgen Del Rocio University Hospital, Spain*
[3]*Biochemistry and Molecular Genetics Department, Hospital Clínic of Barcelona, Spain*
[4]*Biochemistry Department, Institute of Biomedicine of Seville (IBIS), Spain*
[5]*Medical Biochemistry, Molecular Biology and Immunology Department, University of Seville, Spain*

Background

Fucosidosis is a rare autosomal recessive disorder of lysosomal accumulation related to a deficiency in the "alpha-L-fucosidase" enzyme activity, accumulating fucose glycolipids, glycoproteins and oligosaccharides in lysosomes affecting mainly skeleton, central nervous system (CNS), brain, skin and heart. This enzyme is encoded by *FUCA1* (alpha-L-fucosidase1) gene (NM_000147.4), and *FUCA2* (alpha-L-fucosidase2) (NM_032020.4).

Objectives

To propose that the fucosidosis phenotype currently associated with the *FUCA1* gene may also be associated with variants in *FUCA2* alone or in digenic form.

Methodology

DNA was amplified by custom panel for coding regions of 72 genes associated with lysosomal diseases. Sequencing has been performed using the Ion Torrent S5 platform.

Results

We have identified the same homozygous variant of uncertain significance in the *FUCA2* gene, c698CA, (p.Ala233Glu) interpreted as potentially pathogenic variant with AGCM classification criteria.

Patient 1 also was carrier of an insertion of 6 bp in *FUCA2* p.Leu21_Pro22insLeuLeu. Patient 3 had another variant in *FUCA1,* exon 6+1CG; c.1160+1CG potentially affecting the splicing. Alpha-fucosidase activity in leukocytes presented normal values in all patients, but plasma alpha-fucosidase activity was decreased in patients compared to healthy controls.

All patients have compatible symptoms with fucosidosis syndrome: Intellectual disability, hepatomegaly, dermatitis and recurrent infections.

Conclusion

Patient with heterozygous variants in *FUCA1* could be misdiagnosed because *FUCA2* gene is not usually studied. It would be necessary to review these cases and increase the number of cases to consolidate the association of the fucosidosis phenotype to the *FUCA2* gene, either isolated or as a digenic pathology associated with *FUCA1*.

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Rare syndromes

When is Ataxia Etiology Unspecified FragileX-Associated Tremor/Ataxia Syndrome?

Cornelia Lieb-Lundell PT, DPT, MA, Anna M. Edwards PT, DPT, MA, MBA
Physical Therapy, University of St. Augustine for Health Sciences, USA

Background: FragileX-associated tremor/ataxia syndrome (FXTAS) is defined as a late-onset ataxic neurodegenerative disorder that is specific to older male and more recently some female carriers of the pleiotropic gene, FMR1. Patients with FXTAS may experience misdiagnosis, inappropriate or nonhelpful interventions and misdirected referrals before being appropriately diagnosed.

Objective: This poster is designed to demonstrate the differential diagnosis of FXTAS and Ataxia unspecified.

Method: The information was gathered and summarized based on a literature review of Fragile X disorders and Ataxia spanning the years 2015-2022.

Results: FXTAS is a neurodegenerative disorder. The average onset is age 55-60 years with life expectancy 20-25 years from the onset of symptoms. Patients may not be correctly diagnosed before their demise or only diagnosed when a child with FragileX is born within the extended family. Patients may initially be misdiagnosed with Parkinson Disease. Delayed or incorrect diagnosis deprives the patient and family access to appropriate rehabilitative and supportive medical interventions to manage the issues related to neurodegeneration which may include loss of executive function, increased tremor, decreased balance, loss of ambulatory skills, generalized anxiety, etc.

Conclusion: The poster summarizes specific criteria for clinically diagnosing FXTAS. The combination of major and minor criteria is listed to define a definite, probable, and possible clinical diagnosis. Recommendation for patient gene testing should be considered as part of the diagnostic process. Patient and family education will be a central component of planning intervention.

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Rare syndromes

CIC-39Na Reverses Thrombocytopenia and Muscle Damage Characterizing Tubular Aggregate Myopathies

Emanuela Pessolano[1], Beatrice Riva[2], Mauro Vismara[3], Irene P Bhela[1], Tracey Pirali[1], Armando A Genazzani[1]

[1]*Department of Pharmaceutical Sciences, University of Piemonte Orientale, Italy*
[2]*Department of Pharmaceutical Sciences, ChemICare, Italy*
[3]*Department of Biology and Biotechnology, University of Pavia, Italy*

Store-Operated Ca^{2+}-Entry (SOCE) is a cellular mechanism that governs the replenishment of intracellular stores of Ca^{2+} upon depletion caused by the opening of intracellular Ca^{2+}-channels. Gain-of-function mutations of the two key proteins of SOCE, STIM1 and ORAI1, are associated with several rare diseases clustered as tubular aggregate myopathies (TAM). Our group has demonstrated that a mouse model bearing the STIM1 p.I115F mutation recapitulates the main features of these disorders: thrombocytopenia and muscle weakness. At present, no valid treatment is available for these patients.

We evaluated the effect of CIC-39Na a SOCE negative modulator, developed by a spin-off from Università del Piemonte Orientale both in vivo and ex vivo models of TAM demonstrating that the compound is able to counteract the major symptoms of these disorders.

In the present communication, we report the in vivo efficacy of CIC-39Na in restoring platelet number and reducing abnormal bleeding. Subtle differences in thrombopoiesis were observed in STIM1 p.I115F mice, but the main difference between wild-type and STIM1 p.I115F mice was in platelet clearance and in the levels of platelet cytosolic basal Ca^{2+}. Both were restored upon treatment of animals with CIC-39Na.

Moreover, our SOCE inhibitor, CIC-39Na, re-establishes functional motor capacity in vivo and restores SOCE to physiological levels in KI-STIM1^{I115F} derived myotubes.

This finding paves the way for a pharmacological treatment strategy for thrombocytopenia and muscle weakness in patients affected by TAM.

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Rare syndromes

Acquired Hemophilia a Treatment Approach: Case Report

Enisa Zaric[1], Isidora Rubezic[1], Jovana Saban, Sanela Muminovic[2], Marija Djurovic[3]
[1]*Center for Hematology, Clinical Center of Montenegro, Montenegro*
[2]*Primary Health Care Podgorica, Primary Health Care Montenegro, Montenegro*
[3]*Internal Clinic, Clinical Center of Montenegro, Montenegro*

Introduction. Acquired hemophilia A is a rare, life-threatening condition that manifests itself in spontaneous bleeding, mostly in soft tissues. The diagnosis of this disease should be considered in unexplained bleeding, especially in elderly patients.

Case presentation. An 83-year-old female patient was initially hospitalized at the vascular surgery of the Clinical Center of Montenegro due to deep venous thrombosis (DVT) of the right leg. After being discharged from vascular surgery, she noticed a bruise on the skin of her abdomen, for which she was hospitalized again. Surgical drainage of the hematoma in the anterior abdominal wall and tamponade, then new tamponade and revision were performed. During the second hospitalization, the laboratory findings showed anemia with prolonged aPTT values (Er 2.74, Hg 76, MCV 86, D dimer 3.73, aPTT 113.7, PV normal). A reduced level of factor F VIII (0.4 I.U./dl) is found. In a 50:50 mixing study with normal plasma, aPTT and factor VIII did not normalize. The inhibitor level was high (224 BU/mL). The patient was treated with corticosteroids, intravenous immunoglobulins, and therapeutic plasma exchange with factor VII recombinants was performed. There is a gradual stabilization of the laboratory findings as well as the resolution of the hematoma, there have been no repeated manifestations of cowering. Screening tests were carried out in terms of malignancy and autoimmune diseases. The findings of immunoserology indicated a possible systemic connective tissue disease, which was also confirmed by a rheumatologist. She was treated with pulse doses of corticosteroids. The aPTT values remained stable. Due to previously verified DVT, treatment with rivoroxaban was started. Conclusion. Acquired Hemophilia A can be a reversible coagulopathy. Early diagnosis and early initiation of treatment can lead to the successful resolution of the disease. An adequate approach includes screening for the etiology of acquired hemophilia.

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Rare syndromes

Diagnostic and Therapy Approach in Systemic Mastocytosis: Case Report

Enisa Zaric[1], Sanela Muminovic[2], Marija Djurovic[3], Ivana Miketic[1], Ana Stojanovic[1]
[1]*Center for Hematology, Clinical Center of Montenegro, Montenegro*
[2]*Primary Health Care Podgorica, Primary Health Care Montenegro, Montenegro*
[3]*Internal Clinic, Clinical Center of Montenegro, Montenegro*

Introduction: In Systemic Mastocytosis (SM) there is an accumulation of morphologically and immunophenotypically abnormal mast cells in various organs, with or without skin involvement. The clinical course of mastocytosis is heterogeneous ranging from indolent disease to a highly aggressive neoplasm. Bone marrow infiltration is usually asymptomatic, but spine pain and arthralgiae may be present.

Case report: A 70-year-old woman was referred to our Center due to a 4-year-long history of leucopenia. She complains about lumbar spine pain. She had previously established a diagnosis of osteoporosis and Computer tomography (CT) of the skeleton pointed to osteoblastic lesions of the lumbar spine. CT examination of the abdomen showed splenomegaly (150x95 mm), and bone marrow biopsy pointed infiltration with mast cells (CD117, CD25, and mast cell tryptase-positive). Serum tryptase level was elevated (200 ng/ml) and D618V mutation of the KIT gene was confirmed. During diagnostic workup anemia and thrombocytopenia had been revealed in blood count. Our patient was diagnosed with aggressive systemic mastocytosis (SM) according to WHO Classification, group C, although the clinical course of the disease was indolent, without complications for more than 4 years. We started treatment with JAK2/Flt3 inhibitor midostaurin.

Conclusion: Systemic mastocytosis is a rare but well-recognized cause of secondary osteoporosis. Although the identification of the KIT D816V mutation and the emergence of new targeted therapies have significantly improved the diagnosis and treatment of systemic mastocytosis, the diagnosis and treatment of this disease still present challenges.

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Successful Treatment of Rare Malignant Tumor Entity Histyocitic Sarcoma

Enisa Zaric[1], Sanela Muminovic[2], Marija Djurovic[3], Ana Stojanovic[1]
[1]*Center for Hematology, Clinical Center of Montenegro, Montenegro*
[2]*Primary Health Care Podgorica, Primary Health Care Montenegro, Montenegro*
[3]*Internal Clinic, Clinical Center of Montenegro, Montenegro*

Introduction: Histiocytic sarcoma (HS) is an extremely rare malignant neoplasm, accounting for less than 1% of all hemato-lymphoid neoplasms. The tumour cells are derived from monocyte/macrophage lineage and express histiocytic markers, including CD68, CD163, and Lysozyme.

Case report: A 60-year-old man presented with a right-sided neck tumour mass measuring 49mm×39mmx39mm. Microscopy of the lesion revealed a markedly pleomorphic tumour, composed of large cells with vesicular nuclei. Immunohistochemical staining of the tumour cells revealed that LCA S100, CD33, CD68, CD163, CD31, CD4, CD10 and Vimentin were positive.

Radiology evaluation pointed to enlarged nodes at axillae and inguinal regions. Bone marrow biopsy confirmed bone involvement. The patient received systemic chemotherapy (cyclophosphamide, doxorubicin, vincristine, etoposide and prednisone [CHOEP] regimen). After three cycles of chemotherapy, PET CT imaging revealed a hypermetabolic cervical lymph node (21× 24mm), SUV max 21.74. The chemotherapy regimen was changed to ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin). Three cycles of therapy were applied and then an autologous stem cell transplant was performed. Control PET CT revealed hypermetabolic cervical lymph node (10x6x7 mm), SUV max 4,09. Radiotherapy had been applied on the right side of the neck, including radiation at the base of the tumour Control PET CT confirmed remission which persist for two years of follow-up.

Conclusion: HS is an extremely rare malignant neoplasm of the monocytic/macrophage lineage, with no standardized chemotherapy regimen for the multisystemic disease. Metastatic patients have a more aggressive clinical course. High-dose chemotherapy including autologous stem cell transplantation may be an adequate therapy approach.

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Multifocal Periapical Cemental Dysplasia in Periodontal Ehlers–Danlos Syndrome combined with Leukoencephalopathy in the Mutation of c.890G A, G297D [pEDS]

Manfred Nilius[1,2], Minou Hélène Nilius[2], Guenter Lauer[1], Berit Koch[3], Markus Kohlhaas[4]
[1]*Department of Oral and Maxillofacial Surgery, Technische Universität Dresden, University Hospital "Carl Gustav Carus",, Germany*
[2]*Department of Oral and Maxillofacial Surgery, Niliusklinik, Germany*
[3]*Internal Medicine, Privat Clinic, Germany*
[4]*Department of Ophthalmology, St. Johannes-Hospital, Germany*

Abstract

Key clinical message

We describe a case of pEDS with moderate dentition but generalized periapical cemental dysplasia as a possible late sequela and additional cerebral leukoencephalopathy.

Background
Periodontal Ehlers–Danlos syndrome (pEDS; formerly: EDS type VIII) is a rare disorder caused by heterozygous mutations in complement 1 subunit genes C1R and C1S. To date, 148 cases have been described in the literature.
Objectives/Methods

The diagnosis is based on major clinical criteria, including periodontitis with early-onset, persistent pretibial plaques, easy bruising, and a lack of attached gingiva. The minor clinical criteria are joint hypermobility, skin hyperextensibility and fragility, abnormal scarring, and increased rate of infections, hernia, and marfanoid facial features. These criteria consolidate the diagnosis. As a pathognomonic feature, a lack of attached gingiva is assumed.

Periapical cemental dysplasia (PCD) is considered a non-neoplastic proliferation of fibrous tissues and cementum-like hard tissues. PCD is characterized by the presence of vital pulp and is often accidentally discovered by the dentist during a general radiographic survey that presents multiple sclerotic masses affecting the cancellous portion of the jaw and tooth-bearing areas without any clinical signs.

Conclusion

PCD is rarely seen in all four quadrants and, to the best of the authors` knowledge, has not been described as occurring in pEDS. We describe a case of a suspected de novo-mutation of pEDS with generalized PCD and cerebral leukoencephalopathy.

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Rare syndromes

Clinical Trial with the ANGPTL3 Antibody Evinacumab Identifies a New Rare Chylomicronemia Causing Variant in the LPL Gene

Miriam Larouche[1], Robert Pordy[2], Poulabi Banerjee[2], Daniel Gaudet[1]
[1]*Medicine, Université De Montréal and Ecogene-21, Canada*
[2]*Cardiovascular & Metabolism Therapeutics, Regeneron Pharmaceuticals, USA*

Background

Sustained chylomicronemia is caused by lipoprotein lipase deficiency (LPLD) or lack of bioavailability. Sustained chylomicronemia is a rare metabolic disorder characterized by plasma triglyceride (TG) values chronically 10mmol/L. Evinacumab is an angiopoietin like protein 3 (ANGPTL3) monoclonal antibody (mab) with the potential to treat a spectrum of lipid disorders. The efficacy of Evinacumab in decreasing plasma TG levels depends on LPL bioavailability.

Objective

To assess the LPL genotype and drug response in patients with sustained chylomicronemia treated with Evinacumab.

Methods

A phase II clinical trial was conducted with Evinacumab to evaluate its safety and efficacy over 20 weeks in patients with severe hypertriglyceridemia and chylomicronemia. There were 3 cohorts in this study, one of which included patients with sustained chylomicronemia and LPLD. LPL genotypes were assessed in all patients. Plasma TG values were measured at baseline and every 2 weeks for 20 weeks. Genotype-specific response to Evinacumab was assessed by comparing pre-post TG values.

Results

This phase II trial identified one patient being homozygote for an undocumented mutation (E282X) in the LPL gene who did not respond to Evinacumab (TG decrease10% after 20 weeks), which is compatible with lack of LPL bioavailability. This variant is thus suspected to cause LPLD

Conclusion

Clinical trials for rare genetic diseases can reveal new disease-causing gene variants. A phase II clinical trial conducted with Evinacumab, a ANGPTL3mab, in patients with sustained chylomicronemia identified an undocumented E282X mutation in the LPL gene. This new variant is considered as being a LPLD causing (OMIM: 609708).

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Relations between rare diseases and common disorders

The Beneficial Impact of Enzyme Replacement Therapy on Pulmonary Function Abnormalities in Patients with Type 1 Gaucher Disease

Ariel Rokach[1], Nissim Arish[1], Shoshana Revel-Vilk[2], Eli Picard[3], Gabriel Izbicki[1], Ari Zimran[2]

[1]*Pulmonary Institute, Shaare Zedek Medical Center, Jerusalem, Israel; Faculty of Medicine, Hebrew University of Jerusalem, Israel.*

[2]*Gaucher Unit, Shaare Zedek Medical Center, Jerusalem, Israel; Faculty of Medicine, Hebrew University of Jerusalem, Israel.*

[3]*Department of Pediatric pulmonology, Shaare Zedek Medical Center, Jerusalem, Israel; Faculty of Medicine, Hebrew University of Jerusalem, Israel.*

Background: Clinical pulmonary involvement is considered to be rare in type I Gaucher disease (GD1). In a previous study, we found that 68%, of patients with GD1 had abnormal pulmonary function. The aim of this study was to follow such patients over a long period in order to assess changes of pulmonary abnormalities in patients receiving enzyme replacement therapy (ERT) and untreated patients.

Methods: Patients with GD1 followed at Shaare Zedek Medical Center Gaucher Unit, who participated in the original study, were offered follow-up pulmonary function tests (PFT), including spirometry and lung volume measurements using plethysmography. An echocardiogram to detect pulmonary hypertension was performed, and the Tricuspid Insufficiency Gradient (TIG) was measured.

Results: Out of the 95 patients with GD1 who participated in the original study, 58 had follow-up PFT at a median of 10 (3-19) years. PFT showed that: Diffusing Capacity for Carbon Monoxide (DLCO), Forced Expiratory Volume in the first second (FEV1), and TIG were stable but Forced Vital Capacity (FVC), Total Lung Capacity (TLC), and Functional Residual Capacity (FRC) were significantly higher at the end compared to the beginning of the study. At the end of the follow-up period, only TLC values were significantly lower in the untreated patients compared to the treated patients.

Conclusions: This data revealed that abnormal pulmonary functions found in patients with GD1 improved over time, especially in patients on ERT.

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Relations between rare diseases and common disorders

Glycerol as a Correlate of Impaired Glucose Tolerance and Statin-Induced Myalgia: Dissection of Common Complex Systems Using a Rare Mendelian Trait

Josiane Dufour, Diane Brisson, Daniel Gaudet
Département de Médecine, Université de Montréal and Ecogene21, Canada

Background: Glycerol kinase (GK) represents the primary entry of glycerol, an important glucose precursor, into metabolism. We identified a rare X-linked disorder caused by a missense mutation (N288D) in the GK gene. The resulting GK deficiency (GKD) causes severe hyperglycerolemia (glycerol 2.5 mmol/L in men and 0.2 mmol/L in women) associated with an increased risk of impaired glucose tolerance (IGT). Several patients with GKD were under statin therapy. Statin-induced myalgia is common in the general population and can lead to the cessation of treatment. As an osmoprotector, glycerol plays a major role in thermoregulation and resistance to high temperatures, reducing the risk of myalgia or myositis in athletes at risk of rhabdomyolysis, which suggests that glycerol could be involved in muscle toxicity.

Objectives: To evaluate free glycerol level as a marker of IGT or statin-induced myalgia.

Methods: Glycerol concentrations have been measured pre-treatment in 862 patients under statin therapy, including 28 GKD patients.

Results: Statin intolerance correlates with glycerolemia. In non GKD subjects, the prevalence of myalgia was significantly higher among patients with glycerolemia below 0.08 mml/L or above 0.2 mmol/L (p=0.012) (J-curve). A glycerolemia higher than 0.2 mmol/L is associated with a higher risk of statin-intolerance with a CK elevation (odds ratio = 3.71; p=0.02).

Conclusion: These results suggest that glycerol could protect against statin-related muscle damage until a threshold is reached. This study illustrates that a rare genetic disorder (GKD) could be used to improve the understanding of a common trait (statin intolerance).

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Relations between rare diseases and common disorders

Churg-Strauss Syndrome – Rare Disease, False Symptoms, Fatal Consequences: a Case Report

Konstantin Maksin, Tetiana Bocharova[2]
Pathology, Kharkiv International Medical University, Ukraine

Churg-Strauss syndrome (CSS) is a rare condition, affecting 1/1,000,000 patients, morphologically manifests as systemic eosinophilic granulomatous vasculitis. Clinical symptoms resemble bronchial asthma, and serious complications may be overlooked if urgent intervention is needed.

A 43-year-old woman presented at the Hospital Emergency Department with a few days' history of chest discomfort and dyspnoea associated with bronchial asthma which has been treated for many years. She was diagnosed with the status asthmaticus but died with the symptoms of an acute cardio-vascular insufficiency an hour later. Autopsy was performed at the Pathology Department.

Post-mortem examination revealed an acute recurrent myocardial infarction cased death of patient. An acute focal bacterial bronchopneumonia, combined with signs of asthmatic lesions, such as hypertrophy of bronchus muscular wall, were found in the lungs. Histopathological examination indicated that the patient had systemic eosinophilic granulomatous inflammation of the arteries in the heart, lungs, liver and kidneys, accompanied by vascular occlusion, ischemic and necrotic lesions.

Clinical data and post-mortem suggested that the first myocardial infarction, considered by the patient to be an exacerbation of asthma and self-treated, occurred several days before death. The recurrent myocardial infarction and the increase in pulmonary oedema were provoked by bacterial infection. The bronchial asthma and the acute bronchopneumonia masked serious cardiac complications of CSS and prevented urgent intervention.

Family doctors should remember that symptoms of CSS are concealed, manifesting as those of common clinical conditions, and if complications dangerous to life are not considered urgent, the consequences may be fatal.

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Relations between rare diseases and common disorders

Brain Cortical Complexity and Cognitive-Auditory Correlates in Gaucher Disease: Looking for Neurophysiological and Neuropsychological Benchmarks

Maria Giulia Tullo[1], Francesca Caramia[2], Patrizia Mancini[4], Gianmarco Tessari[5], Rosaria Turchetta[4], Giulia Pileggi[1], Francesca Atturo[3], Carlo Di Bonaventura[2], Emanuele Cerulli Irelli[2], Anna Teresa Giallonardo[2], Simona Bianchi[1], Rocco Plateroti[4], Giovanna Palumbo[1], Nicola Monaco[1], Marcella Nebbioso[4], Cecilia Guariglia[5], Fiorina Giona[1]

[1]*Department of Translational and Precision Medicine, Sapienza University of Rome, Italy*
[2]*Department of Human Neurosciences, Sapienza University of Rome, Italy*
[3]*ENT, San Giovanni Addolorata Hospital, Italy*
[4]*Department of Sense Organs, Sapienza University of Rome, Italy*
[5]*Department of Psychology, Sapienza University of Rome, Italy*

The present study, named SENOPRO, extends literature findings on neurological involvement in type 1 Gaucher disease (GD1) by investigating the association between brain cortical complexity (cortical thickness and gyrification) and both neuropsychological and auditory performance in GD1 patients.
Fifteen GD1 (mean age = 43 years, SD = 15 years) and 15 healthy matched controls (HC) without any neurological and psychiatric diseases, underwent a 3T Magnetic Resonance Imaging session including T1 scans. The auditory evaluation was carried out assessing pure the tone audiometry, the speech perception in quiet and in noise with SRT50 IT-MATRIX sentence test. Furthermore, neuropsychological assessment was performed in GD1 patients focusing on language and verbal working memory. A Region of Interest based morphometry analysis was performed by using CAT12 software. By comparing the cortical gyrification (CG) between GD1 and HC in regions involved in language comprehension and production, the CG in the left secondary auditory cortex (LBelt) was significantly reduced in GD1 than HC, whereas the CG in the right frontal region p47r was significantly reduced in HC than GD1 patients. Interestingly, a positive correlation between CG in these regions and the auditory and cognitive performance in GD1 was found. Specifically, the higher the CG the worst the SRT50 outcomes.
In conclusion, these findings on cortical complexity, speech perception and cognition here presented shade light on the specific neurophysiological and neuropsychological correlates in GD patients and will contribute to a better understanding and rehabilitation treatment in this rare disease.

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Relations between rare diseases and common disorders

Evaluating Non-Alcoholic Fatty Liver Disease in Patients with Chylomicronemia Using Fixed or Portable Devices for On-Site and Siteless Visits in Clinical Trials for Rare Diseases

Noémie Audet-Verreault[1], Miriam Larouche[1], Diane Brisson[1], Étienne Khoury[1], Marie-Claude Morissette[1], Daniel Gaudet[1]
MEDICINE, Université De Montréal and Ecogene-21, Canada

Background: Non-alcoholic fatty liver disease (NAFLD) is common in patients with the metabolic syndrome, severe hypertriglyceridemia and chylomicronemia (TG 10 mmol/L) and can be observed in patients with LPL deficiency (LPLD), a rare recessive disease. It is technically possible to evaluate NAFLD and the response to treatment by using fixed or portable devices. Portable devices can be used at-home or for siteless visits in clinical trials for LPLD and other rare diseases.

Objectives and methods. The purpose of this study was to evaluate the expression of NAFLD in subjects with chylomicronemia (TG10 mmol/L) in 38 subjects: 19 LPLD and 19 age and sex matched patients with multifactorial chylomicronemia (MCS). All participants underwent a NAFLD measurement after a 4-hour fast using fixed or mobile elastography (FibroScan®).

Results. NAFLD was observed in 42.1% of LPLD subjects and 73.7% of MCS. Only 25% of FCS subjects with NAFLD had a BMI ≥ 30 compared to 64.3% in MCS (P=0.004). In both cohorts, NAFLD was negatively associated with the risk of acute pancreatitis (p=0.03). Results of elastography were comparable and reproducible whether a fixed or portable device was used.

Conclusion: NAFLD is common in presence of chylomicronemia and tends to be negatively associated with the risk of acute pancreatitis. Portable elastography devices can be used for at-home or siteless visits in clinical studies.

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Relations between rare diseases and common disorders

Refractory Bronchial Asthma Successfully Treated by Mepolizumab in Two Generations of One Family

Shmuel Prints
South District, Clalit Health Services, Israel

Background: Most asthmatic patients are well controlled with treatment by inhaled corticosteroids and bronchodilators. However, approximately 5% of the asthma population couldn’t achieve satisfactory asthma control despite adherence to high-dose inhaler therapies. Early addition of drugs which affect the immune mechanisms of asthma is critical in this group of patients.

Description of the case: This case report describes the course of refractory asthma in a mother and her daughter. Both developed the disease at different times in their adult lives and needed long-term treatment with systemic corticosteroids. Despite the similarity of some of the clinical and laboratory signs of the disease, significant differences in the results of spirometry and the number of eosinophils in the CBC made it difficult to choose biological therapy in the youngest of them.

Results: Treatment with IL-5 inhibitors provided successful and safe asthma control in both patients.

Conclusion: This case illustrates the insufficiency of the current criteria for the selection of biological therapy in refractory asthma patients.

At the same time, it indicates the feasibility of searching for genetic markers to devise precise treatment.

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Relations between rare diseases and common disorders

Genetic Analysis of Families of Patients with Primary Lymphoedema in Slovenia

TANJA Planinsek Rucigaj[2], PETER Korošec[1], JULIJ Šelb[1], Matija Rijavec[1]
[1]*Genetic Laboratory, University Hospital Golnik, Slovenia*
[2]*Dermatovenereological Clinic, University Medical Centre Ljubljana, Tanja Planinsek Rucigaj, Slovenia*

Primary lymphoedema belongs to teh group of rare disease. In Slovenia, the Centre for Lymphology is organized at the DermatovenereologicalClinic, University Medical Centre in Ljubljana as part of the Centre for lymphology, phlebology and chronic wounds. The Centre is connected to the European Network of Rare Disease PPL-VASCERN. It is estimated that primary lymphoedema accounts for around 10% of all lymphoedema. They can appear at the birth, after the first year of life, or they can be part of various syndromes, including those where we find changes in the venous vessels. Rarely, the lymphatic vessels in primary lymphoedema are incompletely develop centrally in the trunc. Today, more than 40 gene mutations are known, in which primary, congenital or sporadic lymphoedemaoccure. In Slovenia, in cooperation with the Genetic Laboratory of the Golnik University Hospital, we carried out genetic studies of families of patients with primary lymphoedema years ago, in which we discovered a new, until then undescribed mutation in the FOXC2 gene.

Poster 80

Role of registries and big data

An Artificial Intelligence-Driven Framework to Screen for HATTR Polyneuropathy by Automatically Detecting Red Flag Symptoms in Electronic Health Records

Dries Hens[1], Lore Wyers[1], Clara L. Oeste[1], **Kristl G. Claeys**[2,3,4]
[1]*Clinical Department, LynxCare, Belgium*
[2]*Department of Neurology, University Hospitals Leuven, Belgium*
[3]*Laboratory for Muscle Diseases and Neuropathies, Department of Neurosciences, KU Leuven, Belgium*
[4]*Leuven Brain Institute, LBI, Belgium*

Background: Rare diseases are often underdiagnosed or diagnosed belatedly. Red flag symptoms have been identified, but their manual screening is a time- and resource-consuming task.
Objectives: This study presents a Natural Language Processing (NLP) algorithm to search for red flag symptoms on Electronic Health Records (EHRs). Using multisystemic hereditary transthyretin amyloidosis (hATTR) polyneuropathy as an example, the study aimed to detect patients at risk that warranted further genetic testing.
Methods: In this retrospective study, a searchable clinical data warehouse was generated by an NLP pipeline with data collected from the University Hospitals Leuven, Belgium. Patients were considered at risk for hATTR if their EHRs had mentions of polyneuropathy or peripheral neuropathy and visited the Neurology Department during the study period (January 2016-January 2021). NLP model performance was assessed on a random sample of EHRs by comparing algorithm outputs to a physician-generated standard.
Results: Out of 1015 total patients, the NLP algorithm detected 128 patients with ≥ 3 red flag symptoms, of which 69 were considered eligible for genetic testing after clinical review. Of these 69 patients, 35 had undergone prior genetic testing and 17 additional patients were identified by the NLP algorithm as eligible, reflecting a relative increase of 48.6% in finding patients at risk of hATTR. Red flag symptoms were detected with high accuracy (F1 scores=0.88-0.98).
Conclusion: Clinically validated NLP algorithms are effective and accurate tools to detect red flag symptoms in EHRs, calling for their use in screening for rare diseases to ease rapid diagnoses and prompt treatment.

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Role of registries and big data

Potentials and Challenges of Health Care Registries in Rare Disease Research – A Danish Cohort Study of Diagnosed Alpha-1 Antitrypsin Deficiency Prevalence, Incidence and Mortality

Emese Vágó[1], John Acquavella[1], Henrik Toft Sørensen[1], Erzsébet Horváth-Puhó[1], Gregory P Hess[1,2]

[1]*Department of Clinical Medicine, Aarhus University and Aarhus University Hospital, Denmark*

[2]*Jefferson College of Population Health, Thomas Jefferson University, USA*

Background

Alpha-1 antitrypsin deficiency (AATD) is an underdiagnosed rare genetic disorder that may manifest in lung or liver symptoms.

Objectives

To estimate the diagnosed AATD (dAATD) prevalence, incidence and mortality between 2000-2018 using data from the Danish health registries.

Methods

We used the Danish National Patient Registry to identify patients diagnosed with AATD based on the International Classification of Diseases (ICD-10) code E88.0A and the Danish Civil Registration System for population counts and vital status. We estimated dAATD prevalence, incidence and compared mortality to an age and sex matched cohort from the general population. We examined the coding changes during 2000-18, from the general E88.0 to the more specific E88.0A ICD-10 code for AATD. We conducted sensitivity analysis to quantify the effect of the switch in coding on the prevalence estimates.

Results

The prevalence of dAATD was 12.9 [95% confidence interval (CI) 11.9, 13.8] per 100,000 persons. The sensitivity analysis indicated that dAATD prevalence might have been as high as 19.7 per 100,000 persons due to less specific ICD-10 coding for AATD early in the study period and 21.4 per 100,000 persons after correcting for left truncation. The diagnosis was more prevalent among males and the age distribution was bimodal, with peaks at ages ≤12 and ≥45 years. Mortality rate was 4.7 (95% CI 4.1, 5.3) times higher for patients with AATD than for the matched general population.

Conclusion

AATD is a rare disease with bimodal age distribution and with increased mortality compared to the general population.

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Role of registries and big data

Brazilian Network for Rare Diseases (RARAS): A National Survey

Ida Vanessa Doederlein Schwartz[1,2,4], Bibiana Mello de Oliveira[1,2], Mariana Lopes dos Santos[1,2], Milena Artifon[1], Júlia Cordeiro Milke[1,2], Amanda Maria Schmidt[1,3], Victoria Machado Scheibe[1,3], Gabriella Zanin Fighera[1,3], Betania Ponce[1], Têmis Maria Félix[1,4], Rede Nacional de Doenças Raras, RARAS[1]

[1]*RARAS, Rede Nacional de Doenças Raras, Brazil*
[2]*Genetics Department, Universidade Federal do Rio Grande do Sul (UFRGS), Brazil*
[3]*Universidade Luterana do Brasil, Universidade Luterana do Brasil (ULBRA), Brazil*
[4]*Medical Genetics Service, Hospital de Clínicas de Porto Alegre (HCPA), Brazil*

Background: The National Policy for Comprehensive Care for People with Rare Diseases was established in Brazil in 2014 and aims to contribute to reduction of morbidity and mortality and improvement of quality of life for Rare Diseases's (RD) patients at the Unified Brazilian Health System. However, national epidemiological data are scarce and restricted to specific disorders.
Objectives: Conduct a survey on the epidemiology of RD of the Brazilian Network for Rare Diseases (RARAS Network).
Methods: RARAS Network was established in 2020 including 18 University Hospitals, 17 RD Reference Services and 5 Neonatal Screening Reference Services throughout all regions of Brazil. A population survey with retrospective data collection (2018-2019) was carried out using a standard protocol.
Results: 12,280 individuals were included (F:50.6%), with a mean age of 21.5 years (±19.33). Most were brown (47.5%), and were born in Northeast (33.4%) and Southeast Brazil (33.3%). A confirmed diagnosis was observed in 63.6%, using biochemical (42.0%) or molecular (30.7%) analysis in most cases. In 123 (1.2%) the diagnosis was performed in the prenatal period. ORPHA code was the terminology used in 64.7% of diagnoses. Family recurrence was reported in 25.4% and consanguinity in 8%. Most (54.2%) underwent specific treatment for RD. A death rate of 1.5% was identified in this period.
Conclusion: This study shows the first Brazilian nationwide data on RD, demonstrating the importance of networking between specialized services. The longitudinal and prospective continuation of this project is warranted, and it is expected it may impact the RD health policy in Brazil.

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Role of registries and big data

The Diagnostic Odyssey of Birt-Hogg-Dubé Syndrome: Insights from the BHD Syndrome International Registry

Katie Nightingale[1], Nina Liu[2], Joshua Henderson[3], Anna Webb[4]
[1]*Charity Officer, The Myrovlytis Trust and BHD Foundation, UK*
[2]*Director of Clinical Product Management, Pulse Infoframe, Canada*
[3]*Head of Rare Diseases, Pulse Infoframe, Canada*
[4]*CEO, The Myrovlytis Trust and BHD Foundation, UK*

Background
Birt-Hogg-Dubé syndrome (BHD) is a rare autosomal dominant disorder associated with mutations in the gene folliculin. It is typified by benign skin tumours (fibrofolliculomas), lung cysts, pneumothorax and kidney cancer. Early diagnosis is critical to reduce the risk of kidney cancer through appropriate surveillance such as regular kidney scans. However, there are no standardised diagnostic or management guidelines for BHD. Therapies are only available to treat the symptoms and there is no cure.

Objectives
To establish an international patient registry to collect information on the diagnosis and natural history of BHD to drive research and improve patient care.

Methods
The Myrovlytis Trust (https://myrovlytistrust.org) and BHD Foundation (https://bhdsyndrome.org) partnered with Pulse Infoframe (www.pulseinfoframe.com) to launch the BHD Syndrome International Registry (BIRT) in March 2022. BIRT was developed through collaboration with patients, clinicians, advocacy groups and industry.

Results
162 people have registered in BIRT of which 101 people have completed the survey. The average age of symptom onset was 30 (interquartile range, IQR 25 – 45). The most common first symptom was fibrofolliculoma (47.5%) or pneumothorax (37.6%). However, average age at diagnosis was 44 (IQR 38 – 52). Reassuringly, the average age at which a person received their first kidney scan was also 44 (IQR 38 – 55).

Conclusions
The large age gap (on average 14 years) between onset of symptoms and diagnosis represents a diagnostic odyssey common to many rare conditions. Raising awareness of BHD, particularly among dermatologists and pulmonologists, and implementing clear diagnostic guidelines may enable earlier diagnosis.

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Role of registries and big data

Expanding our Understanding of Arthrogryposis: The Role of a Pediatric Multisite Registry

Noémi Dahan-Oliel[1,2], Tanya Bedard[3], Haluk Altiok[4], Lauren Hyer[4], Michelle James[4], Cary Mielke[4], Sarah Nossov[4], Jonathan Pellett[4], Ellen Raney[4], Krister Freese[10], Philip Giampietro[5], Harold van Bosse[6], Frank Rauch[1,2], Reggie Hamdy[1,2]

[1]*Orthopedics and Research, Shriners Hospitals for Children, Canada*

[2]*Faculty of Medicine and Health Sciences, McGill University, Canada*

[3]*Genetics, ACASS, Canada*

[4]*Orthopedics, Shriners Hospitals for Children, USA*

[5]*Medical Genetics, University of Illinois at Chicago, USA*

[6]*Faculty of Medicine, Thomas Jefferson University, USA*

Background: Arthrogryposis multiplex congenita (AMC) is an umbrella term including hundreds of conditions with the common clinical manifestation of multiple congenital contractures. AMC affects 1 in 3000 live births and caused by lack of movement in utero. To understand the long-term needs of individuals diagnosed with a rare condition, it is essential to know the prevalence, etiology, and functional outcomes in a large sample. The development and implementation of a multi-center registry is critical to gather this data. This registry aims to improve health through genetic and outcomes research, and ultimately identify new therapeutic targets and diagnostics for treating children with AMC.

Objective: A large-scale registry for children with AMC was implemented to identify causes, risk factors, and the epidemiology of AMC; develop a platform to document interventions and functional outcomes; and determine genetic causes.

Methods: Enrollment occurs in two phases; Part 1 focuses on epidemiology, etiology and interventions. For this part, retrospective and cross-sectional data is collected using a combination of patient-reported outcome and clinical measures. Part 2 focuses on core subset of the study team, including a geneticist and bioinformatician, identifying causative genes and linking the phenotype to genotype via whole genome sequencing (WGS) to identify genetic variants in correlation with pedigree, photographs and clinical information.

Results: Ethics approvals are obtained at eight Shriners Hospitals for Children in North America. Accrual started in October 2019 and now includes 323 children to Part 1. Using Dr. Hall's classification, 77.2% have limb involvement only, 13,5% have limb and other system involvement, and 9,3% have limb and central nervous system involvement. For Part 2, 135 samples had WGS (55 from participants, 80 from family members). Pathogenic or likely pathogenic variants were detected in 52%. Preliminary findings will be presented.

Significance and Conclusion: The systematic collection of genetic and clinical data in a registry allows researchers the opportunity to formulate hypothesis-driven studies on a large, representative sample of children with AMC. Identifying causative genes will facilitate diagnosis, personalized treatment, and the provision of genetic counselling to families.

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Role of registries and big data

Unsupervised Independent Component Analysis in Newborn Screening

Tomáš Adam[1,2,6], Štěpán Kouřil[1], Julie de Sousa[1,3], Kamila Fačevicová[3], Alžběta Gardlo[1], Christoph Muehlmann[4], Klaus Nordhausen[5], David Friedecký[1,2]

[1]*Department of Clinical Biochemistry, University Hospital Olomouc, Czech Republic*

[2]*Laboratory of Metabolomics, Institute of Molecular and Translational Medicine, Palacký University Olomouc, Czech Republic*

[3]*Department of Mathematical Analysis and Applications of Mathematics, Faculty of Science, Palacký University Olomouc, Czech Republic*

[4]*Institute of Statistics & Mathematical Methods in Economics, Vienna University of Technology, Austria*

[5]*Department ofMathematics and Statistics,, University of Jyväskylä, Finland*

[6]*Department of Laboratory Methods, Faculty of Health Care of the Slovak Medical University in Bratislava, Slovakia*

Background: Newborn screening LC/MS data are traditionally analyzed based on “supervised” reference ranges established on prior knowledge of the disease biomarker behavior and percentile statistics.

Objectives: A new approach to the processing of newborn screening LC/MS data using unsupervised multivariate independent component analysis (ICA) is presented and compared to traditional approach.
Methods: Disease free controls group of 10213 individuals and 77 patients suffering from nine different diseases have been analyzed in discovery study in order to visualize the clustering of individual groups of patients into specific ICA components. A validation study consisting of 150 controls and 20 patients was calculated using IC loadings from the discovery data to confirm the ability of the method to diagnose new IEM patients.
Results: ICA detected all patients (5SD cut off criteria applied) in the discovery and validation parts of the study.
Conclusion: The results demonstrated the potential use of this method as an alternative approach in routine newborn screening.

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Single gene diseases

Systematic Review and Pooled Analysis of Genetic of Anaplastic Thyroid Carcinoma

Elian Santos, Geisa Xavier Souza, Aparecida Sousa
Department of Biomedicine, UNIFG, Brazil

Anaplastic thyroid cancer (ATC) is the rarest and extremely aggressive thyroid cancer composed of undifferentiated tumor cells with poor prognosis and resistant to common thyroid cancer therapy. ATC may originate de novo or by transformation of preexisting differentiated thyroid cancer as papillary thyroid carcinomas to ATC, that has been describe by the presence of commons mutations. In this study, we aim to evaluate the outcome of genetic analysis of anaplastic thyroid carcinoma origin perform a systematic review concerning and pooled analysis of gene association. A systematic review using the MEDLINE/Pubmed and Cochrane databases was performed. Data from all eligible studies were extracted, and a pooled analysis of literature was carried out to record the genes and genetic associations involved. As a result, the molecular pathogenesis of ATC includes mutations in BRAF, RAS, CTNNA1, PIK3CA, TP53, AXIN1, PTEN 14, E1F1AX and TERT mutations were detected in 43%, 25%, 10%, 18%, 66%, 9%, 20%, 14%, 69% respectively. Interaction between different gene mutation has been suggested to be the main causative factor for origin of ATC and the concomitant BRAF/RAS and TERT, mutations were associated with worse outcome than mutation in only one of the genes, in addition, in the metastases analysis (nodal and distant), mutations with similar frequency were observed in BRAF and RAS. Although ATC is a rare disease, there is currently a consistent amount of information about the genetic mutations most frequently associated with this tumor.

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Single gene diseases

A Rare Case of Neurodegeneration with Brain Iron Accumulation: Neuroferritinopathy

Caroline Grimon[1], Christophe Lemey[1], **Michel Walter[1]**, Douraied Ben Salem[2], Boris Chaumette[3], Florian Stephan[1]

[1]CHU Brest University Psychiatry, Rte de Ploudalmézeau, 29820 Bohars, France
[2] CHU Brest University Neuroradiology, Bd Tanguy Prigent, 29200 Brest, France
[3]Center for Rare Psychiatric Disorders, GHU Paris Psychiatrie et Neurosciences, INSERM U1266, Université Paris Cité, Paris, France

Background: Syndromes with neurodegenerations with brain iron accumulation (NBIA) are a group of neurodegenerative disorders of rare monogenic genetic diseases, related to abnormalities of intracerebral iron homeostasis, by excess iron mainly in the globus pallidus and adjacent areas.

One of these rare disorders is neuroferritinopathy caused by mutations in the FTL1 gene (ferritin light polypeptide) yielding abnormal configuration of the ferritin molecule and accumulation of toxic unbound ferrous iron. This genetic mutation follows an autosomal-dominant pattern of inheritance with high penetrance. The prevalence of this pathology remains unknown and less than 50 cases have been reported worldwide. The disease appears around 40 years of age, revealed by movement disorder, including chorea, ataxia and oromandibular movements, with cognitive and psychiatric disorders.

Case report: We present a case of a 44 years old female with prominent psychiatric features including behavioural defects, reversal of circadian rhythm and irritable behaviour evolving for two years, associated with orofacial tics since the age of 25. All the biological tests were negatives. The neuropsychological evaluation was not in favour of frontotemporal dementia. Brain MRI showed increased iron loading in the globus pallidus, substantia nigra and the red nucleus. The patient was initially treated for late-onset schizophrenia with Quetiapine 300mg with a limited reduction in her irritability, and improvement in sleep.

Conclusion: Neurologic and psychiatric features dominate the symptomatology in neuroferritinopathy. Clinical suspicion should lead to brain MRI and genetic testing to confirm the diagnosis. There is no specific treatment to date, and the current treatment remains symptomatic.

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Single gene diseases

Can Mutations in a "BIOFUEL" Enzyme IDI LEAD to Autism?

Chen Liang, Hanfeng Lin, Sandipan Roy Chowdhury, Lang Ding, Feng Jin, Xiaoli Qi, Jin Wang

Pharmacology and Chemical Biology, Baylor College of Medicine, USA

Isopentenyl Diphosphate Delta Isomerase (IDI), or Isopentenyl pyrophosphate isomerase (IPP isomerase), activity was first detected in Saccharomyces cerevisiae. This enzyme catalyzes the isomerization of Isopentenyl pyrophosphate (IPP) to its highly electrophilic form dimethylallyl pyrophosphate (DMAPP). A heterozygous missense mutation (229 AT) in IDI was detected in a boy with autism phenotypes. To investigate the role of IDI in autism, we cloned the IDI gene with the same missense mutation and purified the mutant IDI protein (M20L). The subsequent enzyme activity assay using LC-MS showed lowered catalytic activity of M20L. This indicates a deficiency in IDI activity might be associated with autism phenotypes of the boy. Future directions will include establishing an IDI haploinsufficiency mouse model to validate the function of IDI and a drug screen to enhance M20L activity.

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Single gene diseases

Utility of Whole Exome Sequencing in Diagnosis and Management of Rare and Previously Undiagnosed Conditions: 2-Year Single-Center Experience

Katerina Slaba[1], Petra Pokorna[2], Petra Pokorna, Dagmar Prochazkova, Dagmar Prochazkova[1], Petr Jabandziev[1], Petr Jabandziev, Ondrej Slaby[2], Ondrej Slaby
[1]*Department of Pediatrics, University Hospital Brno, Faculty of Medicine, Masaryk University, Czech Republic*
[2]*CEITEC & Faculty of Medicine, Masaryk University, Czech Republic*

Background: Whole-exome sequencing (WES) has been demonstrated to increase diagnostic yield in pediatric populations and improve treatment options.
Objectives: This study aimed to use WES in patients with undiagnosed diseases and evaluate the diagnostic yield and the clinical impact of such an approach on patient care in the Czech population.
Methods: Patients from the Department of Pediatrics, University Hospital Brno, Czechia, were recruited for our prospective study. Eligible pediatric patients had a rare undiagnosed disease with a high likelihood of a genetic cause with uninformative targeting testing or were critically ill in the ICU. In total, 28 probands and 26 of their parents were enrolled, consented to participate, and underwent WES and/or targeted Sanger sequencing (in parents).
Results: Among the symptoms were psychomotor retardation and other neurological symptoms (n=12), dysmorphic features (7), GIT symptoms, failure to thrive (11), unexplained laboratory findings (9), and acute renal failure (1). Overall, 47% (13/28) of probands had a pathogenic or likely pathogenic variant identified in a gene associated with their primary indication for testing, of which 6 had an autosomal recessive mutation (ALDOB, PMM2, NPHP1, ABCC8, SGSH, TJP2), six autosomal dominants (PPP2R5D, EXT1, KCNQ2, MYRF-siblings, DYRK1A), and 1 X-linked (PHKA2). Out of these findings, eight variants (29%) were medically actionable results leading to the change in patient care.
Conclusions: Based on our 2-year experience, WES facilitated the diagnostic process and improved patient care in an undiagnosed pediatric population. We believe it is an effective approach to enable appropriate counseling, surveillance, and management strategies.

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Extensive Identification of Genes Involved in Congenital and Structural Heart Disorders and Cardiomyopathy

Nadine Spielmann, Valérie Gailus-Durner, Martin Hrabe De Angelis
German Mouse Clinic, Institute of Exoerimental Genetics, Helmholtz Munich, Germany

Background: Clinical presentation of congenital heart disease is heterogeneous, making identification of the disease-causing genes and their genetic pathways and mechanisms of action challenging.

Objectives: In this study, we used 3,894 single-gene knockout mouse lines (null deletion alleles) produced by the International Mouse Phenotyping Consortium (IMPC) for an unbiased discovery of genes with monogenic heart disease phenotypes.

Methods: We identified structural and functional cardiac abnormalities in adult mice by clinical in-vivo electrocardiography and transthoracic echocardiography. Moreover, ex-situ iodine-contrast high spatial resolution microcomputed tomography imaging of embryo hearts was applied to reproduce known, and identify hitherto unknown genes, that as null alleles had congenital monogenic cardiac rhythm disorders, cardiomyopathies, and structural heart defects.

Results: Our study identified 705 genes with cardiac rhythm disorder, myocardial hypertrophy, and/or ventricular dilation phenotypes, 70% of which (486) have not to our knowledge been previously linked to cardiac function or cardiac disease. Among those 705 genes, 486 have not been previously associated with cardiac dysfunction in humans, and some of them represent variants of unknown significance (VUS). Mice with mutation in Casz1, Dnajc18, Pde4dip, Rnf38, or Tmem161b genes show developmental cardiac structural abnormalities, with their human orthologues being categorized as VUS. Using the UK Biobank data, we validate the importance of DNAJC18 gene for cardiac homeostasis, by showing that its loss of function associates with altered left ventricular systolic function.

Conclusion: Our results identify hundreds of previously unappreciated genes with potential to detect rare disease variants with implications in monogenic congenital heart disease.

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The Value of Knockout Mouse Models in Rare Diseases Research

Patricia Da Silva Buttkus[1], Nadine Spielmann[1], Helmut Fuchs[1], Valerie Gailus-Durner[1], Martin Hrabě de Angelis[1,2,3]

[1]*Institute of Experimental Genetics, German Mouse Clinic, Helmholtz Zentrum München, Germany*

[2]*German Center for Diabetes Research, Helmholtz Zentrum München, Germany*

[3]*TUM School of Life Sciences, Technische Universität München, Germany*

Background: Rare diseases (RDs) are challenging for medicine because of heterogeneous clinical manifestation and low prevalence. There is a lack of specific treatments and only a few hundred of the approximately 7.000 described RDs have an approved treatment. Knockout (KO) mouse models have proved an important *in-vivo* asset to understand the causality of genes by allowing standardized research into the pathogenesis of diseases.

Objectives: We exploit comprehensive, systemic phenotyping data obtained from single-gene KO mutants in the German Mouse Clinic (GMC) for research into RDs.

Methods: Single-gene KO mice were generated and analyzed systematically covering a broad range of tests to identify phenotypes. Parameters from mutant homozygotes were statistically compared with those from wild-type mice of the same background strain.

Results: We show KO mouse models that are not only proprietary genes like proof-of-concept RD targets (*Nacc1, Bach2, Klotho alpha*), moreover we focus on recognized RD genes with no pre-existing KO mouse models (*Kansl1l, Acsf3, Pcdhgb2, Rabgap1, Cox7a2*). Additionally, we present yet unknown genes (*Zdhhc5*) with phenotypic data not presently associated with known human RDs suggestive of causal genes underlying for undiagnosed diseases.

Conclusion: We stage genes that, when deleted, cause differences in the mouse organ-wide, providing a huge translational potential for further understanding monogenic RDs and their clinical spectrum. The GMC, partner of the International Mouse Phenotyping Consortium, is generating new mouse models for phenotyping characterisation. From our 20-years' experience, the clinical community values the genetic KO studies in mice to explore the critical physiological mechanisms and its overall therapeutic potential.

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Sickle Cell Retinopathy in Children- Not So Rare

Pooja Soni, Bhavna Dhingra, Samendra Karkhur, Narendra Chaudhary
Department of Pediatrics, Department of Ophthalmology, All India Institute of Medical Sciences (AIIMS), India

Background: Sickle cell disease is most common inherited blood disorder. Vaso-occlusion, leading to various manifestations involving various organs including eyes, most common and sight threatening being retinopathy. Proliferative retinopathy leads to neovascularization, and makes prone for vision loss. This manifestation can be managed if diagnosed early and vision loss can be prevented. This study was conducted in children (7-18 years) with sickle cell disease to diagnose retinopathy by using Ocular coherence tomography (OCT).

Objectives: To evaluate prevalence of Sickle Cell Retinopathy by Optical Coherence Tomography in children (7-18 years) in Central India.

Methods: This cross-sectional study was performed in children with sickle cell disease (both homozygous and compound heterozygous forms) of 7-18 years age who did not have any visual symptoms. Complete ophthalmological examination including OCT (macula and optic disc measurements) using Cirrus HD-OCT was performed. Results of OCT were compared with normograms for similar age children.

Results: Among 48 participants, all had normal visual acuity, abnormal fundoscopy finding (NPSR) was found in 3 patients (6.25%), thinning of central macula in 3 patients (6.25%), thinning of inner macula in 6 patients (12.5%), thinning of outer macula in 1 patient (2%), RNFL thinning in 3 patients (6.25%), GCL-IPL thinning in 7 patients (14.5%). Overall NPSR was found in 6.25% detected with fundoscopy, while retinal layer thinning was found in 20.8% patients using Ocular Coherence Tomography.

Conclusion: Early diagnosis of retinopathy in SCD affected individuals can prevent sight threatening complications. The need for regular screening for these complications cannot be overemphasized.

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SIGMAR1 Gene Mutation Causing Distal Hereditary Motor Neuropathy and Juvenile ALS in Two both Children of Same Family. A Case Report

Reyhane Parvin[1], Leila Sadat Mohamadi Jahromi[2], Rouholah Hakimian[3], Hasan Moradian[4]
[1]*Department of Physical Medicine and Rehabilitation, Shiraz University, Iran*
[2]*Department of Physical Medicine and Rehabilitation, Shiraz University, Iran*
[3]*Department of General Surgery, Shiraz University, Iran*
[4]*Department of Animal Science and Genetics, Shahid Bahonar University of Kerman, Iran*

SIGMAR1 gene encodes a non-opioid endoplasmic reticulum (ER) protein involved in many cell functions and is expressed ubiquitously in both central and peripheral nervous systems. Alterations of its normal function may contribute to two phenotypes: juvenile amyotrophic lateral sclerosis (ALS) and distal hereditary motor neuropathies (dHMN). We present two cases from a family, a male patient, of 21 years old, with distal muscle weakness and atrophy beginning in adolescence and slowly progressive in some months recent before of referring for an electrodiagnostic study. Neurological examination revealed a symmetrical severe muscle wasting and weakness in distal lower and upper limbs, with claw hands, foot drop with equinovarus deformity and hammer toes, generalized areflexia, and normal sensory examination. The electrodiagnostic study demonstrated a pure chronic motor peripheral nerve involvement without signs of demyelination. And his sister complained of spasticity gait and slowness of movement in addition to the weakness of lower limbs with generalized deep tendon reflex brisk with clonus in the bilateral ankle. The electrodiagnostic study revealed chronic denervation–reinnervation in both upper and lower limbs with normal motor and sensory nerve conduction study; in two cases. Finally, the molecular study found the deletion c.561_576del on exon four and the deletion of all exon 4 in the SIGMAR1 gene.

Keywords: SIGMAR1 gene, juvenile ALS, distal hereditary motor neuropathy.

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Mutational Spectrum Causing Usher Syndrome in a Cohort of Mexican Individuals

Vianey Ordoñez-Labastida[1,2], Jesus Lima-Barrientos[2], Oscar Chacon-Camacho[1,2,4], Juan C Zenteno[1,2,3]

[1]*Rare Disease Diagnostic Unit, Faculty of Medicine, National Autonomous University of Mexico, Mexico*

[2]*Genetics, Institute Of Ophthalmology Conde De Valenciana, Mexico*

[3]*Biochemistry, Faculty of Medicine, National Autonomous University of Mexico, Mexico*

[4]*School of Medicine, FES Iztacala National Autonomous University of Mexico, Mexico*

Background

Usher syndrome (US) is a genetically heterogeneous rare disorder characterized by retinitis pigmentosa and sensorineural hearing loss. US has a prevalence of 3.2 to 6.2 cases per 100,000 and is the main cause of deaf-blindness. So far, mutations in 16 genes have been identified in 3 disease types which are classified according to hearing and vestibular phenotypes. Mutational analysis of US patients from different ethnicities will allow a better characterization of the molecular spectrum of the disease.

Objectives

To describe the mutational spectrum leading to US in a cohort of Mexican individuals.

Methods

The study population comprised patients with a clinical diagnosis of US syndrome evaluated at the Institute of Ophthalmology Conde de Valenciana, Mexico City, and who were demonstrated to carry biallelic variants in US genes. Medical records were reviewed to collect clinical information and all patients underwent DNA sequencing using either a panel of 330 genes causing retinal dystrophies or whole exome sequencing.

Results

A total of 56 patients from 48 families were identified. 64% of cases (n=36) were caused by mutations in *USH2A*, 17% (10) in *MYO7A*, 7% (4) in *CDH23*, 4% (2) in *ADGRV1*, 4% (2) *CLRN1*, and 4% (2) in *PCDH15*. Overall, 50 different variants were demonstrated with 18 of them being novel mutations.

Conclusion

Eighteen novel variants in genes associated with US were identified, thus expanding the mutational spectrum. Molecular diagnosis is important for diagnosis, prognosis and individualized management and is becoming particularly relevant with the arrival of potential therapies for US-related genes.

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Clinical Value of 4E-BP1, p4E-BP1, eIF4E and VEGFR in Perivascular Epithelioid Cell Tumours (PEComa)

Aleksandra Zielińska[1], Julia Sołek[1], Anna Szumera- Ciećkiewicz[2], Tomasz Świtaj[3], Anna M. Czarnecka[3], Piotr Rutkowski[3], Marcin Braun[1], Hanna Romańska[1]
[1]*Departament of Pathology, Chair of Oncology, Medical University of Lodz, Poland*
[2]*Departament of Pathology and Laboratory Diagnostic, Maria Sklodowska-Curie National Research Institute of Oncology, Poland*
[3]*Department of Soft Tissue/Bone Sarcoma and Melanoma, Maria Sklodowska-Curie National Research Institute of Oncology, Poland*

Background

Perivascular epithelioid cell tumours (PEComa) are rare mesenchymal neoplasms originated from epithelioid perivascular cells expressing both smooth muscle and melanocytic markers. Most of PEComas are benign, and curable with surgery. Malignant PEComas occur sporadically and, as there are no valid diagnostic criteria for malignant behaviour, they still pose a diagnostic and therapeutic challenge. mTORC1/4EBP1 pathway is a key molecular driver of PEComa's malignant progression, thus an immunohistochemical assessment of its components (4E-BP1, p4E-BP1, eIF4E, VEGFR) may prove valuable in tumour prognostication.

Objective

To analyse the utility of 4E-BP1, p4E-BP1, eIF4E, VEGFR in the diagnosis of malignant PEComas in relation to the routinely assessed histopathological features.

Methods

Formalin-fixed paraffin-embedded tissue of angiomyolipoma (AML, n=8) and PEComa-NOS (not otherwise specified, n=13), were stained immunohistochemically for 4E-BP1, p-4E-BP1, VEGFR2, eIF4E. The expression levels were quantified according to the semiquantitative H-score approach. Collected data were analysed statistically.

Results

Expression levels of 4E-BP1, eIF4E, VEGFR, but not of p4EBP1, were higher in PEComa-NOS than AML (p0.001, p=0.034, p=0.003, p=0.670). Tumour cellularity was associated with high expression of 4E-BP1 and VEGFR (p=0.006, p=0.007). VEGFR level was negatively correlated with a number of mitoses (p=0.053;R=-0.43), and it was higher in cases with necrosis (p=0.011). In PEComa-NOS, eIF4E level correlated negatively with a number of mitoses (p=0.067;R=-0.54).

Conclusion

Expression levels of 4E-BP1, eIF4E, VEGFR vary significantly between PEComa-NOS and AML and are associated with pathological features of malignancy. This suggests that their evaluation might assist in the routine diagnostic and prognostic assessment of the tumours.

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Neonatal Cholestasis - Need to Think and Look Beyond

Bhavna Dhingra[1,2], Anchal Tripathi[1,2], Priyanka Ahirwar[1,2], Mahesh Maheshwari[1,2]
[1]*Pediatrics, All India Institute of Medical Sciences, India*
[2]*Pediatrics, All India Institute of Medical Sciences, India*

Background: A variety of conditions can present as neonatal cholestasis. Mitochondrial DNA depletion syndromes (MTDPS) are a heterogenous group of disorders caused by mutations in multiple genes responsible for maintenance of mitochondrial DNA (mtDNA). MPV17 loss-of-function may result in tissue-specific nucleotide pool alterations, decreased mitochondrial folate levels and rise in mtDNA uracil levels.
Objectives/ Case Details: A 7-month-old male, 5th born to a non-consanguineous couple presented with yellowish discoloration of eyes and clay-colored stools for 2 months and abdominal distention for 10 days. There were 4 sibling deaths, within first year of life, with similar presentation. Patient was icteric, edematous with abdominal distention, generalized hypotonia, hypertrichosis, brachycephaly, closed anterior fontanelle with long and flat philtrum and SAM. There was hyponatremia and hypocalcemia, elevated LDH conjugated hyperbilirubnemia transaminitis, hypoalbuminemia,coagulopathy and lactic acidemia. Tandem mass spectrometry showed increased methionine. Patient had persistent hypoglycemia requiring a GIR 10 mg/kg/min and ultimately succumbed.

Methods Clinical exome revealed homozygous missense variation in Exon 7 of the MPV 17 mutation (chr2:g.27311899CG; Autosomal recessive, ACMG- likely pathogenic), confirming the diagnosis of mitochondrial DNA depletion syndrome. Parental segregation studies could not be done due to financial constraints.
Results Family was counselled regarding the prognosis, mode of inheritance and need for prenatal diagnosis in future pregnancies.

Conclusions- A strong family history and availability of genetic diagnosis helped clinch a rare diagnosis in a common clinical condition encountered frequently.

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The Study of the Peculiarities of Liver's Adaptive-Compensatory Mechanisms at the Initial Stage of Subdiaphragmatic Vagotomy

Diana Dzidziguri, Nino Kharaishvili, Merab Tchanturia, Tornike Gogolauri
Biology, Ivane Javakhishvili Tbilisi State University, Georgia

Background: Classically, during liver regeneration in response to resection, mass recovery occurs through hepatocyte proliferation, hypertrophy, and polyploidization. But in various pathologies, without mass loss, the compensatory-adaptive growth of the liver does not always proceed with these strictly regulated sequential mechanisms of regeneration. It's known that the Vagus nerve stimulates liver regeneration and after the termination of Vagus innervation, regeneration processes in the liver are delayed.

Purpose: Our work's goal was to study the peculiarities of liver's adaptive-compensatory mechanisms at the initial stage of subdiaphragmatic vagotomy.

Research object- adult, white rats, model- subdiaphragmatic vagotomy and partial hepathectomy, material- liver tissue.

Methods: staining of slices with hematoxylin-eosin, staining of smears with Fiolgen's reagent, determination of DNA with program Image.

Results: Our studies have shown that at 22 h after subdiaphragmatic vagotomy the number of cells with high DNA content and to be specific 8c and 4cx2 cells are increased, without an increase in mitotic index. This fact allows us to assume that the multiple increase of DNA concentration in mononuclear octaploid hepatocytes is achieved by activating alternative -endoreplication mechanism. And the generation of 4cx2-binuclear octaploid cells by endomitosis.

Conclusion. An increase in the number of both 4Cx2 and 8C cells at the initial stage after subdiaphragmatic vagotomy indicates that the genome fold increase in the liver is achieved by simultaneously activating two different mechanisms.

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The Adaptive Mechanism of Liver in Response to Hyperglycemic Functional Stress in Alloxan Induced Diabetes

Diana Dzidziguri, Eka Bakuradze, Merab Tchanturia, Merab Sepashvili, Tornike Gogolauri, Giorgi Aleksanashvili, Nino Kharaishvili
Biology, Ivane Javakhishvili Tbilisi State University, Georgia

Background: It's true diabetes is not rare disease but it represents a serious medical and social-economical problem because of its spread level and effects on disablement and life expectancy. Recent studies and research have shown a decrease of high ploidy (2c×2) hepatocytes within one month of injection of alloxan or streptozotocin drug in Diabetes mellitus experimental models. The described phenomenon can be explained by a decrease of insulin concentration, which controls cytokinesis, and accordingly the amount of high ploidy cells during cytoskeleton reorganization. Nevertheless, the changes in correlation between diploid and high ploidy cells is not investigated at the initial phase of disease (within the first 48 hours) when extreme changes in glucose concentration are indicated.

Methods: staining of slices with hematoxylin-eosin, staining of smears with Fiolgen's reagent, determination of DNA with program Image, Immunohistochemical analysis.

The aim: The aim of the presented work was to study the adaptive mechanism of the liver in response to hyperglycemic functional stress at the initial stage of diabetes

Results: It was found that in 48 hours after alloxan injection there is no significant change in hepatocyte mitotic activity. Nevertheless, the amount of 4c cells in liver is significantly increased (p0.05)

Conclusion: Formation of high ploidy hepatocytes (presumably G2-0 population) without changes in proliferation activity in response to increased functional stress on liver during initial phase (within the first 48 hours) of alloxan induced diabetes (white adult rat experimental model) is an adaptive peculiarity of the organ.

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Erdheim-Chester Disease, Presenting with Bilateral Hydronephrosis

Elena Zakharova[1], Olga Vorobyeva[3], Eugene Nikitin[2]
[1]*Nephrology, Botkin Hospital, Russia*
[2]*Hematology, Botkin Hospital, Russia*
[3]*Rare Diagnosis, National Centre of Clinical Pathology Diagnostics, Russia*

Background: Erdheim-Chester disease is a rare non-Langerhans histiocytosis associated with MAPK pathway mutations; less than 1000 cases reported so far. Typical presentation includes sclerotic bone lesions, central diabetes insipidus, restrictive pericarditis and retroperitoneal fibrosis. Diagnosis is based on clinical features, imaging and histopathology, identification of BRAF mutations important to guide targeted treatment.

Objectives: To report a case of Erdheim-Chester disease, diagnosed by histopathology of retroperitoneal tissue, and confirmed by identification of BRAF-V600 mutation.

Methods: 63-years old Caucasian female presented 6 years prior to admission with a loin pain, bilateral enlargement of kidney pelvises and calyces, and declined urethral stents placement. At admission, she complained on decrease of urine output; her serum creatinine was 301 μmol/L, kidney ultrasound revealed bilateral urethral enlargement and hydronephrosis, CT showed massive retroperitoneal infiltration. She underwent bilateral percutaneous nephrostomy and perirenal tissue biopsy; her kidney function dramatically restored, and histopathology demonstrated diffuse histiocytic infiltration (CD68+/CD1α-/S100-) with marked xantomatous transformation, and concomitant desmoplastic fibrosis. Full-body FDG-PET-CT confirmed infiltration of perirenal tissue and pelvises, and found changes of the femoral and tibiae bones.

Results: The patient was diagnosed with Erdheim-Chester disease, started on interferon alpha; genetic tests were ordered and identified BRAF mutation – c.1799 TA, p. (V600E), which confirmed the diagnosis. Interferon alpha was discontinued, the patient was recently started on the targeted treatment with vemurafenib.

Conclusion: Erdheim-Chester disease can present without any bone pain just with hydronephrosis, caused by specific perirenal infiltration; characteristic long bones involvement can be quiescent and discovered only after establishing of the diagnosis.

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Cryptococcus neoformans osteomyelitis in Tibia. A Rare Case

Georgios Gourtzelidis[1], Dimitrios Pallis[1], Kalliopi Diamantopoulou[2], Kleoniki Georgousi[3], Ioannis Aifantis[1], Stamatios Papadakis[1]

[1]*B' Department of Orthopedics, KAT General Hospital of Attica, Greece*

[2]*Pathology Department, Kat General Hospital of Attica, Greece*

[3]*Department of Internal Medicine, Kat General Hospital of Attica, Greece*

Osteomyelitis is a bone inflammation that can be related to various infectious agents. Fungal osteomyelitis is rare and usually found in immune-compromised patients. Very few cases of Cryptococcus osteomyelitis have been reported so far.

A non-HIV female patient, 82 years old, visited the Emergency Department due to a 3-day pain located mainly over the anterior surface of the tibia, accompanied by swelling and redness. Her past medical history reveals rheumatoid arthritis treated with methotrexate and corticosteroids. Initial imaging with an X-ray showed an osteolytic area in the upper third of the tibial diaphysis. The patient was hospitalized and underwent a CT-guided biopsy. The specimen was cultivated and revealed a Cryptococcus neoformans infection of the bone. She underwent surgical debridement of the lesion with local application of amphotericin B. She was also treated with 400 mg fluconazole twice a day for three weeks while in hospital and 200 mg twice a day upon discharge for a 6-month duration. She is closely monitored in our outpatient office and the inflammation has regressed completely.

All in all, our patient was immune compromised due to corticosteroid treatment for rheumatoid arthritis as well as methotrexate, a known Disease Modifying Anti-Rheumatic Drug. There was a referred close contact with pigeons, a main host container of the disease. The patient responded well in antifungal pharmacotherapy and surgical debridement. The most usual finding was the bifocal nature of the infection, affecting both the tibia and the breast.

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Case Report: A Novel Variant in *SLC25A46* Causing Sensorimotor Polyneuropathy and Optic Atrophy

Louise Sloth Kodal[1], Sophia Hammer-Hansen[2], Sonja Holm-Yildiz[1], Tina Dysgaard[1]
[1]*Copenhagen Neuromuscular Center, Department of Neurology, Rigshospitalet, Denmark*
[2]*Department of Clinical Genetics, Rigshospitalet, Denmark*

SLC25A46 is a mitochondrial protein involved in mitochondrial dynamics and has recently been identified as a pathogenic cause in a spectrum of neurological syndromes. We report a novel homozygous *SLC25A46* variant in two Danish siblings, originally from Iraq. Patient A had since childhood experienced sensibility disturbances lateral in upper extremities and tingling and prickling sensation in the lower extremities and a general "weakness" when carrying heavy objects as well as impaired balance. Patient B described herself as healthy except for a medical history of migraine with aura and progressively decreased vision since the age of ten until the age of 25, where she experienced increasing problems with balance and tendency to leg cramps. Both were diagnosed with optic atrophy in childhood, but had never received diagnostic clarification. The neurological examination and nerve conduction studies were consistent with sensorimotor polyneuropathy. Patient A having a mild polyneuropathy and Patient B a pronounced polyneuropathy. The cases illustrate the spectrum of the disease and provide substantial information to the knowledge of polyneuropathy caused by *SLC25A46* variants. It further highlights the possibilities of whole genome sequencing which can improve future understanding of disease mechanisms.

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Psychomotor Improvement in a Patient with Collagen VI-Related Myopathy Following Liver Transplantation

Matea Kovacic Perica[1], Nedo Marcinkovic, Nedo Marcinkovic, Nedo Marcinkovic[1], Jurica Vukovic, Jurica Vukovic[1,2]
[1]*Department of Pediatrics, Division of Pediatric Gastroenterology and Hepatology, University Hospital Centre Zagreb, Croatia*
[2]*School of Medicine, University of Zagreb, Croatia*

CASE PRESENTATION:

Three months old, female infant was referred to us because of suspected cholestatic jaundice. Jaundice, hepatosplenomegaly, ascites, hypotonia with muscle atrophy, distal joint laxity, and facial dysmorphia were present. She was secondborn to unrelated, healthy parents with unremarkable family history. Upon investigation, hepatic vein thrombosis with narrowing of the intrahepatic segment of inferior vena cava and combined thrombophilia were revealed. Diagnosis of congenital Budd-Chiari syndrome (BCS) was established and treated with low-molecular-weight heparin. Liver function deterioration due to biopsy-proven advanced cirrhosis was observed, as well as progressive sarcopenia and hypotonia despite physical therapy. At the age of 16 months, she had poor head control, couldn`t sit unassisted, and didn`t talk.

BCS caused liver failure, but it couldn`t explain the psychomotor delay, myopathy, and dysmorphic features, so we opted for genetic testing. The molecular karyotype was normal.

Whole exome sequencing revealed a de novo heterozygous missense mutation in the *COL6A3* gene coding for collagen VI, classified as a variant of unknown significance. Mutations in the *COL6A3* cause a spectrum of disorders with muscle and connective tissue involvement, with Ullrich Congenital Muscular Dystrophy (UCMD) as the most severe form.

At 17 months, successful cadaveric split liver transplantation was performed. Subsequently, there was a significant psychomotor improvement, and within three months, she gained head control, could sit unassisted, and started to talk.

CONCLUSION:

Patient with features of collagen type VI-related myopathy and congenital BCS had a rapid and significant psychomotor improvement after successful liver transplantation.

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Ethical aspects in rare diseases

Rare Diseases: Common Gen (Ethics)?

Natália Oliva-Teles[1,2,3,4]
Centro de Genética Médica Doutor Jacinto Magalhães (CGM), Centro Hospitalar do Porto (CHUPorto), 4099-001, Portugal
MEDCIDS, Departamento Medicina da Comunidade, Informação e Decisão em Saúde, Faculty of Medicine, University of Porto, Portugal
UMIB, Unidade Multidisciplinar de Investigação Biomédica, ICBAS - Instituto de Ciências Biomédicas Abel Salazar, Universidade do Porto, Portugal
ITR, Laboratory for Integrative and Translational Research in Population Health, Porto, Portugal, Portugal

Background: According to the WHO, rare diseases (RD) are “illnesses that affects a small percentage of the population, thereby limiting scientific research, clinical expertise and patient access to effective treatment options.” RD may disturb 3.5% - 5.9% of the global population, thus affecting nearly 300 million people worldwide (1). About 72% of RD are genetic whilst others are the result of infections, allergies and environmental causes (https://www.eurordis.org/). A very relevant systematic review was made in 2021 on genetic/genomic testing to define the parameters for ethical, legal and social implications (ELSI) (2), enhancing the need to develop national regulation on personalized genomic medicine. Objectives: To reinforce the need to dedicate special attention to RD genetic data sharing for research. Conclusion: In spite of complying with Good Clinical Practice, Regulation (EU) 2016/679 regarding the protection of natural persons with regard to the processing of personal data and the free movement of such data, obtaining Informed Consent (Declaration of Helsinki) and assuring confidentiality of all information of selected participants, little special attention is “dedicated” to RD research, whose patients are keen to share their data but are physically very disperse in the world. The promotion of an “European Health Data Space”, a health specific ecosystem comprised of rules, common standards and practices, infrastructures and a governance framework may be the right direction to attend this need. References: (1) doi: 10.1080/01443615.2018.1519693; (2) doi.org/10.1186/s12910-021-00720-5. Acknowledgments: UMIB/ICBAS/UP, supported by National Funds through the FCT in the frameworks of the UIDP/00215/2020 and UIDB/00215/2020.

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Metronomic Cyclophosphamide and Metastatic or Non-Resectable Soft Tissue Sarcomas: Further Assessment of Efficacy and Safety

Clément Bolognini[1], Pauline Simon[2], Fabien Calcagno[1], Alice Hervieu[3], Isabelle Desmoulins[3], Sylvain Causeret[4], David Thibouw[5], Elsa Kalbacher[1], Guillaume Meynard[1], Loïc Chaigneau[1]

[1]*Medical Oncology Department, CHU Jean Minjoz, France*
[2]*Pediatric Onco-hematology Department, CHU Jean Minjoz, France*
[3]*Medical Oncology Department, Centre Georges-François Leclerc, France*
[4]*Surgical Oncology Department, Centre Georges-François Leclerc, France*
[5]*Radiotherapy Department, Centre Georges-François Leclerc, France*

Context and aims:

Metronomic Cyclophosphamide's use in monotherapy as a palliative treatment against non-resectable and metastatic Soft Tissue Sarcomas (mSTS) relies on small retrospective cohorts' data. We need external validation of its efficacy and safety profile in these settings of usually frail patients. We assessed further data and aimed to identify predictive factors of metronomic cyclophosphamide impact in mSTS.

Methods:

We analysed retrospectively a multicentric cohort of mSTS patients treated with metronomic cyclophosphamide 50 mg twice daily, with or without steroids, in 2 French regions. The primary outcome was Progression-Free Survival (PFS), and secondary outcomes were Response Rate (RR), Overall Survival (OS), and Toxicity.

Results:

We analysed 60 patients' data treated between 2005 and 2021, with 33 above 65 years, including 21 in first or second therapeutic line. The median PFS was 2.7 months (range 0-28), median OS 6.9 months (range 0-50), and RR was 5%, with an additional 15% Stable Disease (SD) over 12 weeks. Among patients over 65 years in first or second therapeutic line, median PFS and OS were 3.8 (0-10) and 7.7 months (2-28), RR was 9%, with an additional 19% SD over 12 weeks. Twenty-seven percent of patients experienced adverse events of any grade, without any above grade II. Steroids' adjunction negatively impacted PFS and OS, while sarcoma's radio-induced nature did not. We identified no predictive factor of toxicity.

Conclusion:

Metronomic Cyclophosphamide is an active and well-tolerated treatment option in mSTS. Further data are however still needed to predict treatment activity and determine the exact regimen to use in these settings.

Keywords: Sarcoma; Soft Tissue Sarcoma; Cyclophosphamide; Administration, Metronomic; Palliative Care

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Culler Jones Syndrome (CJS) - A Rare Syndrome with a Rare Presentation

Karishmah SenthilKumar, Radhalakshmi Senthil, Soundaram Karthik
Paediatric Department, Apollo Children's Hospital, Chennai, India

Background

CJS is a rare autosomal dominant disorder occurring due to a mutation in the GLI2 gene on chromosome 2q14 characterised by hypopituitarism and/or polydactyly. Some patients present with development delay, cleft/lip palate, cryptorchidism, micropenis and/or short stature. These patients are prone for epilepsy, psychomotor retardation and poor dentition.

Method:

We present a second born to a diabetic mother with an antenatal diagnosis of Tetralogy of Fallot (TOF). At birth, he was noted to have cryptorchidism and a postnatal ECHO confirmed TOF. At 21 days of life, his prolonged Jaundice screen picked up hypothyroidism TSH 6.40 IU/ml. In view of cryptorchidism and micropenis further endocrine evaluation revealed multiple pituitary hormone deficiencies. MRI Brain showed an absent anterior pituitary gland and stalk with an ectopic posterior pituitary. Currently his major concern is persisting growth failure.

Result:

Clinical exome sequencing revealed GLI 2 mutation, confirming a diagnosis of CJS. Now at 16 months, he weighs 6.8kg with a height of 65cm which is below the third centile according to the Indian growth charts highlighting significant growth retardation. His face is also very small with a depressed nasal bridge.

Conclusion:

CJS has a highly variable phenotype. The disorder shows incomplete penetrance and variable expressivity. Cardiovascular complications have not been associated with CJS, however our patient had TOF which could be significant to the syndrome. GLI2 mutation should be suspected in patients presenting with congenital hypopituitarism, cryptorchidism and micropenis. Early diagnosis leads to better management and outcomes. This helps predict the course of illness.