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2-3 July 2018 | London, UK

The International Congress on Advanced Treatments in Rare Diseases

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Poster Board #1

Defective Function of KCa3.1 Channels in Lysosomal Storage Disorders (LSD)

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The calcium-calmodulin-gated KCa3.1 is a key regulator of membrane hyperpolarization, maintenance of cellular electrolyte balance, Ca^{2+}-signalling, secretion of pro-inflammatory cytokines, neurodegeneration, pathological tissue remodelling. Osteonecrosis/-penia, vasculopathies, and neurodegeneration are chronic and progressive inflammatory complications of several inherited LSD: (Gaucher Disease (GD1/GD3), Fabry Disease(FD), and Niemann-Pick disease type C1 (NPC1). We have hypothesized that KCa3.1 functions are impaired in patients' fibroblasts or the monocyte/macrophages lineage. A total of 25 subjects were analyzed (5 FD, 5 NPC, 5 GD1, 5 GD2, 5 healthy controls). For patch-clamp experiments, cells were seeded on coverslips and used within 24 h. Monocytes isolated and purified from peripheral blood from age-matched GD patients (GD1 and GD3) and healthy volunteers. Measurements were repeated in patient's and controls macrophages that were differentiated from monocyte precursors *in vitro* by exposure to erythrocyte lysates for 4 days. Ca^{2+}-activated K^+ currents were measured in the whole-cell configuration (EPC10-USB amplifier) and a K pipette solution (intracellular) containing 1 µM Ca^{2+} free (in mM): 140 KCl, 1 $MgCl_2$, 2 EGTA, 1.71 $CaCl_2$ (1 µM [Ca^{2+}]free). For data acquisition and analysis we used the patch-master program (HEKA).

Patch-clamp demonstrated lower fibroblast KCa3.1 membrane functions in NPC1 and male FD patients. KCa3.1-currents in monocytes were similar in GD-1/3 and controls. In differentiated and activated macrophages, the overall larger KCa3.1 currents in GD-1 macrophages were reduced to 40% of controls while in GD-3 macrophages KCa3.1 currents were barely detectable. Glucosylceramide was found to produce KCa3.1-current desensitization. At the gene level, KCa3.1-mRNA expression was impaired in NPC1, GD1/3, and male FD patients.

Defective KCa3.1 functions are a feature and biomarker of cellular dysfunction in the LSD, GD1/3, FD, and NPC1 and supports the concept that biased lipid metabolism harms ion channel functions. Pharmacological targeting of KCa3.1 could be therapeutic utility to achieve neuroprotection in GD3 and NPC1 patients.

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Poster Board #2

Upstream of precise disease models for better downstream decision making

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Inborn errors of metabolism are a common cause of inherited diseases. Diseases of carbohydrate metabolism pathway include lysosomal storage diseases (LSDs), which are a significant subgroup with approximately 70 LSDs. Grouped according to their defective lysosomal proteins and pathways they are usually characterized by intralysosomal accumulation of substrate. Accumulation may occur at different levels in diverse types of cells, some of which are of difficult access. Patient, molecular, cell and tissue heterogeneity hinders the development of further therapeutic approaches.

We are currently establishing human Induced Pluripotent Stem Cells (iPSCs) from fibroblasts of LSDs patients and controls. The use of disease-specific cell models, mimicking the cell-target of the specific disease, may help to appropriately study the pathogenesis as well as the therapeutics. Integrating new techniques in the work pipeline for the establishment of models may lead to more accurate models while ensuring the safeguard of the patient's background.

Advanced technologies like microarray and NGS profiling add to the traditional techniques such as Immunofluorescence, directed sequencing and conventional cytogenetics. As in the diagnosis process, we may better understand the prognosis, and contribute to cost avoidance, by combining genomic and protein profiling checkpoints in the cell-model establishment pipeline.

The investment in the upstream checkpoints might prove to be helpful in ensuring the integrity of the cell models.

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Poster Board #3

First imprints of two novel biomarkers for Pompe Disease (LSD) in plasma and urine in comparison to Glc4 in urine

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Pompe disease is an autosomal recessive glycogen storage disease type II with acid-α-glucosidase deficiency. Patients affected with this disease are unable to degrade glycogen stored in the lysosome and this leading to the accumulation of glycogen mostly in lysosomal storage vacuoles. The incidence is approximately 1 to 40.000 live births. The diagnosis is still challenging as there is almost no biomarker for determination of the severity and progression of the disease phenotype. Today, only Hex4 or more in detail Glc4, a four sugar unit in urine, can give some hints: Sometimes Glc 4 is a useful marker, sometimes it remains with rather unclear levels. Our search for novel biomarkers in Pompe disease started about four years ago and different attempts had no outcome. In a highly intensive check of human plasma with HPLC-MS (Orbitrap) and HPLC-ELSD, especially fitted for sugars, we found very encouraging results. With this knowledge we checked in a pilot study plasma and urine samples of 19 adult genetically proven Pompe patients in comparison to 10 healthy people. The outcome was two unique novel biomarkers fitting for plasma/serum but also for urine. Now these biomarkers will be applied systematically to further samples. A comparison with the until now “best biomarker for Pompe” (Glc4 in urine) will be presented.

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Poster Board #4

Severe idiopathic bradykinin-mediated angioedema with neurological symptoms and acute myocardial infarction: a special case study.

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Background
Acquired autoimmune non-histaminergic bradykinin-mediated angioedema is a rare disease. It is result of increased vascular permeability.

Objective
Reporting a rare case of angioedema.

Method
A 40-year-old female with autoimmune hypothyroidism. She presented severe recurrent angioedema with breathing difficulties and stridor. Later, she was admitted with confusion and loss of strength in the left half of her body in the context of an angioedema attack. Anyway, she suffered another attack, and epinephrine and methylprednisolone were administered by the ambulance physicians. During the ambulance trip she started to feel oppressive pain in the centre of the chest radiating to the back. The electrocardiogram showed sinus tachycardia and minimal J-point elevation in all the leads. In the hospital, she was diagnosed with myocardial damage, related to the epinephrine treatment. Afterwards, icatibant, a competitive bradykinin antagonist, was added as emergency treatment and an improvement occurred after 15 minutes.

Results
A thorough blood test and a study of complement proteins were performed, with no findings. There was no factor XII mutation.

Conclusion
The above case is that of a patient with autoimmune disease who presented various life-threatening episodes of severe angioedema. On the other hand, the response to immunosuppressive drugs could suggest an autoimmune origin. As the prognosis in these cases is very serious. On the other hand, such a good response to icatibant suggests a bradykinin-mediated.

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Poster Board #5

Novel Mutation in SCYL1 Gene Causes Aberrant Splicing in a Family with Recurrent Episodes of Liver Failure and Cerebellar Ataxia

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Background
Mutations in the SCYL1 gene might be involved in multi-organ dysfunction mainly affecting liver and nervous systems. To date, only 10 patients were described with a wide variability in genotype and phenotype.

Objective
We describe two members of one family with recurrent episodes of hepatic failure, cerebellar ataxia, peripheral neuropathy and short stature. Liver transplantation was considered. Whole Exome Sequencing revealed a novel synonymous mutation in a splicing site of the SCYL1 gene.

Methods
Whole exome sequencing (Trio) revealed a new variant in exon 4 of SCYL1:c.459CT p. (Gly153Gly) which did not appear to affect the protein sequence. Silico prediction analysis suggested that this modification could alter the SCYL1 mRNA splicing processing. The SCYL1 mRNAs in our patient's lymphocytes were analyzed and aberrant splicing was found.

Conclusion
This case emphasizes the importance of synonymous variants in the pathogenesis of the disease. Mutations in the SCYL1 gene should be included in the differential diagnosis of patients with impaired liver function and neurological symptoms, particularly if cerebellar involvement is suspected.

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Poster Board #6

Why rare diseases are not so rare - Epidemiological reasons for orphans underestimation

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Statement of the Problem

Prevalence is an epidemiological measure that is mostly used to define orphan diseases. Health policy makers and the industry base their decisions regarding the importance of the disorder to the public health, by its ***periodic prevalence***. ***Point prevalence*** helps physicians determine the likelihood of a patient is ill with a certain disease. In the case of orphan diseases, the presumptive low prevalence leads doctors to reject a rare diagnosis in favour of other diseases.
The use of prevalence to estimate the rare diseases burden, does not consider pitfalls in its calculation.

Methodology & Theoretical Orientation

The infamous journey towards a rare diseases diagnosis is known as the "diagnostic odyssey". Late diagnosis leads to the patient`s erroneous long registration in the information system under the title of a dandruff disorder. Additionally, it delays a definitive treatment to the patient with a rare disease, and therefore may shorten their life span.
These effects directly impair the assessment of orphan diseases by their prevalence. The point prevalence is particularly hurt. As a result, the doctor`s judgment in the diagnostic process is impaired too.
Underestimated prevalence of the rare diseases population causes a slowdown in the development of its recognizing and treating options and so, contributes to diagnostic delay.

Conclusion

Fast and accurate diagnosis of orphan diseases is the key to solving the complex problems of rare disease patients.

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Poster Board #7

Advantages and disadvantages in organizing strategy for rare diseases in small countries

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Objective
Establishing rare diseases as a special group of diseases started in early 80`s, and many objectives were considered so far. Although diverse in origin, these diseases have many items in common: awareness of their existence in medical circles; difficulties in recognition; expensive diagnostic procedures and few therapeutic possibilities. Many countries develop strategies for management the patients with rare diseases according the legislative and possibilities. In small and developing countries this task meets additional obstacles in organizing action plans.

Materials and methods
A working group organized by Ministry of health was set up where different profiles of specialists were integrated, as well as expert from health policy making. After determining the Program, strategies for diagnosing and registering rare diseases were established. Funding policies were established by the authorities. The diseases were divided into two groups: those for whom treatment is provided by the government, and those only for registration. The system of registration has been developed according international guidelines, including all data from adjacent patient organizations for neurologic, syndromic, hematologic diseases, etc.

Discussion
In small and developing countries organization of services for rare diseases meet additional difficulties. Making the strategy for registering patients with RD have its advantages and disadvantages, including organization of the service, funding for diagnostic procedures and recent therapeutic possibilities etc. Centralized gathering data for patients and registration that include personal information, clinical and laboratory records through sophisticated system provides collection of data and precise estimation of prevalence of patients with rare syndromes in the country, and can help in planning the funds and human resources. Establishing regional bonds between neighboring small countries with limited resources and diagnostic possibilities is helpful for better organization and patient care.

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Poster Board #8

Innovative FOX3 gene transfer based therapy approaches to treat IPEX Syndrome, prototype of autoimmune monogenic disease.

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FOXP3 is a key transcription factor for the maintenance of immune tolerance. *FOXP3* mutations result in dysfunction of FOXP3+ regulatory T cells (Tregs) causing Immune dysregulation, Polyendocrinopathy, Enteropathy, X-linked (IPEX) syndrome, a severe early onset autoimmune disease, which can be fatal if not promptly diagnosed and treated. Our recent international study analyzing the long-term outcome in 96 IPEX patients of the two currently available treatments, pharmacological immune suppression and allogeneic hematopoietic stem cell (HSC) transplantation, showed poor long-term disease-free survival or overall survival limitations, respectively (Barzaghi F. et al, JACI, 2018). IPEX syndrome is a good candidate for gene therapy as it has been demonstrated that reconstitution of wild-type Treg cells can control the disease. Lentiviral-mediated (LV) FOXP3 gene transfer successfully converts IPEX patients-derived CD4+ T cells into Treg-like cells ($CD4^{LV\text{-}FOXP3}$ T cells) with stable suppressive capacity (Passerini L. et al, Sci Transl Med, 2013). These *ex vivo* converted Tregs are ideal as a short term cell-based therapy for IPEX patients, but this approach does not re-establish regulated FOXP3 expression in Teff cells, that also likely contribute to the IPEX pathology. To provide more effective treatments for IPEX patients, we are i) optimizing LV-FOXP3 gene transfer in T cells to be suitable for clinical use, and ii) establishing a novel *FOXP3* gene editing in HSCs and testing both approaches in preclinical models. Thus, we are further characterizing $CD4^{LV\text{-}FOXP3}$ T cells and, at the same time, developing gene editing strategies for IPEX, whereby autologous T cells or HSCs are genetically modified or corrected, respectively, and reinfused into the patients.

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Poster Board #9

Lysosomal Acid Lipase (LAL) deficiency - Wolman disease

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Lysosomal acid lipase (LAL) deficiency is an autosomal recessive inborn error of metabolism with a wide spectrum of clinical features ranging from mild to severe, depending on the activity level of the enzyme. The most severe phenotype is the infantile form, known as Wolman disease. LAL deficiency produces fat accumulation in the visceral organs, causing malabsorption, growth failure, liver failure, adrenal fat desposition and calcification. This results in death by the age of one year.

We present a 4-months old girl, who was admitted to the hospital due to failure to thrive, abdominal distention and vomiting. Physical examination revealed a prominent abdomen and hepatosplenomegaly. Laboratory findings included normocytic anemia, elevated aminotransferases, elevated total cholesterol and triglyceride levels with prominently low HDL. Abdominal X-ray showed bilateral adrenal calcifications.

Based on the clinical, laboratory and imaging studies, Wolman disease was suspected. Diagnosis was confirmed by a dried blood spot test showing undetectable LAL activity. Sequencing analysis on the LIPA gene showed homozygous variant c.206GT p(Gly87Val).

Upon diagnosis, treatment was started with recombinant human lysosomal acid lipase (Kanuma - Sebelipase alfa). She was fed with parenteral low fat solution in addition to a low fat formula given by nasogastric tube. Six months later, laboratory results are improving; she is gaining weight, and developing properly.

In conclusion - Wolman disease is a rare metabolic disorder, with characteristic radiologic and laboratory findings. High index of suspicion in similar clinical settings will lead to early diagnosis. Prompt initiation of enzyme substitution therapy is important, since it improves prognosis.