

PRECEPTORSHIP PROGRAMME ON RARE DISEASES:

MUCOPOLYSACCHARIDOSIS, MANAGEMENT AND TREATMENT

Zentrum für seltene Erkrankungen (ZSE)



November 2nd, 3rd, 4th, 2015

Zentrum für seltene Erkrankungen
Wiesbaden, Germany

Organizers:

Dr. med Christina Lampe
and Prof. Maurizio Scarpa, MD PhD



THE CENTER FOR RARE DISEASES AT THE HELIOS DR. HORST SCHMIDT KLINIKEN WIESBADEN

The Center for Rare Diseases at the Children's Hospital of the HSK in Wiesbaden opened on January 1st, 2014.

The HSK is part of a network of 111 clinics, which are owned by Helios, the largest hospital operator in Europe. The HSK is a hospital of maximum care with 22 specialist clinics and 4 institutes (in total 1021 beds) localized in Wiesbaden (near Frankfurt). The Children's Hospital of the HSK has 110 pediatric beds and 2 intensive care units. The Hospital offers all assessments needed to take adequate care for patients with multisystemic diseases.

There is already a full neurological workup with all needed assessments available as well as a very experienced pediatric neurosurgical unit. During the last 2 years, more than 15 MPS patients (mostly MPS I, IV and VI) received decompression surgery of the craniocervical junction inside the pediatric clinic of the HSK. Here the pediatrics have already a lot of experience with rare diseases, in fact, the HSK is one of the certified centers for patients with tuberous sclerosis and other neurological disorders.

The Center for Rare Diseases is part of the Children's Hospital of the HSK in collaboration with all other Clinics of the HSK that are needed for the management of multisystemic and progressive diseases. The Center for Rare Diseases is the site of the Brains for Brain Foundation, German Branch.

Beside organizing a multidisciplinary rare disease team, we want to facilitate and speed up diagnosis, management and treatment for national and international rare disease patients, improve the patients and their families' quality of life and be an elective meeting point for stakeholders as well as establishing a basic and clinical research unit for neurometabolic diseases, in particular Lysosomal Storage Diseases (LSDs), which is the major responsibility of the Brains for Brain Clinical Research Institute.

An educational programme, so called "The Preceptorship Programme", concerning rare diseases including customized presentations, seminars, meetings, journal clubs, scientific evenings etc. has been designed to increase awareness knowledge and interest in rare diseases and network between the Center and other clinical sites in different countries in order help them anytime in solving potential problems in the management of LSD and neurometabolic patients.

The Center for Rare Diseases at the HSK has been funded on January 2014. It is the first non-university Rare Disease Center in Germany. In order to follow the recommendations of the National Action Plan for Rare Diseases in Germany (published August 2013) aimed at the establishment of a structure of certified Centers, the Center is in collaboration with all other rare disease centers in Germany.

PROPOSAL FOR AN EDUCATIONAL PRECEPTORSHIP PROGRAMME IN MPS

WHY A PRECEPTORSHIP PROGRAMME

FACTS

- a) MPSs are rare diseases present worldwide with similar penetrance in different countries. Only in countries where consanguinity is allowed they may be epidemiologically more represented.
- b) MPSs may have severe and attenuated phenotypes, the latter receiving a delayed diagnosis and present mostly in adult patients.
- c) MPSs are followed generally by pediatric metabolic physicians, adult patients may encounter some difficulties in being followed due to the lack of training and awareness of adult-treating physicians on rare diseases.
- d) Therapies (i.e. ERT) are now becoming available for a growing number of diseases in a wider number of countries inside and outside Europe.

EMERGING PROBLEMS

- a) Therapies availability is not always followed by an adequate technical knowledge or awareness by medical and paramedical professionals even in centers where it is administered. This is present in some European countries but in particular in those countries where the concept of "rare disease" has been only recently acquired, such as East European and Mediterranean countries.
- b) Patients may be exposed to risks of potential severe adverse events due not to the drug itself but rather to the scarce knowledge about preparation and administration of ERT at paramedical and medical levels. This may represent a risk for interruption of therapies for the patient, which may be avoided if a proper training and knowledge is available.
- c) Adult patients affected by MPS may not be followed properly for the lack of expertise by adult-treating physicians due to the not so uncommon defective awareness that rare diseases may be present also in adult patients. For this reason, adult patients may not be taken in charge by any specialist but rather only by general practitioners.
- d) Scarcity of expertise and lack of awareness in paramedical and medical professionals add a further burden to the ones already due to the chronicity of the disease, further deteriorating the quality of life of the patients.



OUR STRATEGY TO IMPROVE MANAGEMENT, THERAPY AND QUALITY OF LIFE OF PATIENTS: THE PRECEPTORSHIP PROGRAMME

AIMS

Our proposal is aimed at:

Facilitating the training and awareness about MPS and their therapies in paramedical and medical professionals to create a new class of professionals able to manage and treat properly MPS patients.

Action:

The Professionals will be hosted at the Center and the training will be performed by face to face meetings.

The training will be divided in theoretical and practical units.

- a. Theoretical Training: Medical and paramedical personnel will be addressed with lectures regarding MPS explaining the clinical history, progression, pathophysiology, management and treatment, discussion on management of therapy related reactions and prevention of reactions.
- b. Practical training: The Medical and Paramedical Personnel will follow the Center's personnel in the visits of patients and will evaluate medical records, imaging, neurophysiological test, ultrasounds, etc.

EXPECTED RESULTS:

- 1) To facilitate the knowledge of paramedical and medical professionals trained by experts in management and treatment of MPSs.
- 2) To ensure the safety the initiation of therapies in patients from countries where there is not experience of administration.
- 3) To decrease the possibility of severe adverse events during treatment and help patients to receive a state of the art follow up.
- 4) To give the opportunity to discuss therapy even in patients coming from non specialised centers and establish a connection with the treating doctors and nurses.
- 5) To create a network of professionals linked to the training hospital to guarantee medical and technical counselling even after the training.
- 6) To facilitate the follow up of patients by evaluating the status of the disease.

Dr. med. Christina Lampe, MD, PhD

Prof. Maurizio Scarpa, MD, PhD

PRECEPTORSHIP PROGRAMME

November 1st 2015

ARRIVAL AND GET TOGETHER DINNER

15.30-16.00

The Ear Nose and Throat in MPS
ANNEROSE KEILMANN, Bad Rappenau DE
discussion and experience of the guests

16.15 Coffee

16.45-18.00

Case presentation from guests and discussion

Dinner

November 3rd 2015

Clinical Management of MPS
and case discussion

9.30-10.00

Neurology of MPS
MAURIZIO SCARPA, Wiesbaden DE
discussion and experience of the guests

10.15-10.45

Neuroimaging and MPS
RENZO MANARA, Salerno IT

10.45-11.15 Coffee

11.15-11.45

Neurosurgery and MPS
MANFRED SCHWARTZ, Wiesbaden DE

11.45-13.00

Discussion of cases from participants

13.00-14.30 Lunch

14.30-15.00

Orthopedic problems in MPS
ANDREA BORGIO, Padova IT
discussion and experience of the guests

November 2nd 2015

9.30

Welcome and aim of the meeting
MAURIZIO SCARPA, CHRISTINA LAMPE
and the International Office of HSK, DE
Introduction of the participants

Clinical Management of MPS
and case discussion

10.00-10.30

Classification and pathophysiology of MPS
CHRISTINA LAMPE, Wiesbaden DE
Discussion.

11.15-11.45

Genetics and epidemiology of MPS
MICHAEL BECK, Mainz DE
Discussion.

12.00-12.45

Experience from the guests

12.45-13.45 LUNCH

14.00-14.30

Respiratory problems in MPS
WOLFGANG KAMIN, Hamm DE
discussion and experience of the guests

14.45-15.15

Anesthesiology problems: discussion
of MPS cases
CHRISTINA LAMPE, Wiesbaden DE
discussion and experience of the guests



November 4th 2015

15.15-15.45
Cardiology and MPS
CHRISTOPH KAMPMANN, Mainz DE
discussion and experience of the guests

16.00-16.30 Coffee

16.30-17.00
Ophthalmological problems in MPS
JOCHEN WAHL, Wiesbaden DE
discussion and experience of the guests

17.15-18.00
Discussion of cases from participants

18.00-18.30
Living with MPS, a personal experience
ALEXIA ZIMMER, Königstein, DE

Dinner

ERT experiences and troubleshooting

9.30-10.45
ERT, principle and procedures
FLORIAN LAGLER, Salzburg AT

10.45-11.15 Coffee

11.15-11.45
ERT safety
CHRISTINA LAMPE, Wiesbaden DE

11.45-12.15
Discussion

12.15-13.00
ERT, Immunology and management of side effects
CHRISTINA LAMPE, Wiesbaden DE
General discussion and summary

13.30 Lunch and leaving the course

SPEAKER BIOGRAPHIES

MAURIZIO SCARPA



Prof. Maurizio Scarpa is the Director of the Centre for Rare Disease at the Helios Horst Schmidt Klinik (HSK) in Wiesbaden, Germany, and Professor of Pediatrics at the University of Padova, Italy. He received his medical degree, pediatric residency and doctorate from the University of Padova. He completed a postdoctoral fellowship at the European Molecular Biology Laboratory (EMBL) Heidelberg, Germany, on Molecular Biology and Gene Expression and at the Howard Hughes Medical Institute, Institute for Molecular Genetics, Baylor College of Medicine, Houston, TX, USA, on genetics and gene therapy. He has extensive expertise as a basic scientist in genetics, biotechnology, metabolic diseases and as a clinician in the diagnosis and treatment of paediatric rare disorders. Together with Prof. David Begley, Kings College London, UK, he is the Founder and President of the Brains for Brain Foundation (www.brains4brain.eu), a Paneuropean Research Foundation, grouping more than 60 international Universities and 10 Biotech Companies, collaborating to the development of therapies crossing the blood brain barrier and the understanding of basic mechanisms of rare pediatric neurodegenerative disease.

CHRISTINA LAMPE



MD, is Vice Director of the Center for Rare Diseases Department of Paediatric and Adolescent Medicine at Helios Dr. Horst Dr Horst Schmidt Kliniken GmbH in Wiesbaden, Germany. After studying medicine at the Humboldt-University of Berlin (Charité), Germany, she completed her internship at the Surgical Department of the same University. Since 2007, she is consultant in surgery. During 2007, she first worked in a surgical private practice and then changed to Villa Metabolica, at the Department of Pediatric and Adolescent Medicine, University Medical Center of the Johannes Gutenberg-University of Mainz, Germany. She worked there as the attending physician for 150 pediatric and adult patients with MPS I, II, IV and VI. In January 2014, together with Prof Maurizio Scarpa, she has set up a Center for Rare Diseases at the Dr Horst Schmidt Clinic in Wiesbaden. She was a coinvestigator on the Phase 3 trials in mucopolysaccharidosis type IV (MPS IV –Morquio syndrome) and the Re-Survey Study in MPS VI (Maroteaux-Lamy), Dr Lampe also is an investigator for the Hunter Outcome Survey and the MPS VI Clinical Surveillance Program (CSP). Dr Lampe is a member of the Natural History Working Group in MPS II, the Steering Committee in MPS II, and the CSP Publishing Board. One of the authors of the 2011 European recommendations on the diagnosis and multidisciplinary management of MPS II, Dr Lampe's research has also appeared in journals such as, *Journal of Inherited Metabolic Disease*, *Rheumatology*, *Molecular Genetics and Metabolism* and *Orphanet*.

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Scientific Officer: Cinzia Maria Bellettato, PhD

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Coauthor of guidelines regarding the diagnosis and management of MPS, she is particularly interested in the craniocervical compression and related symptoms, a major neurological complication present in particular on MPS I, IV and VI patients. Member of several boards and advisory council on MPS she has described a severity score system for the grading of spine-cervical complication in MPS IV and VI.

Christina Lampe's interests are also devoted to correction of multiplex dysplasia in collaboration with orthopedicians for the creation of customized supports for the management of spine malformations, joint problems and hip dysplasia.

Dr Lampe is Scientific Advisor for the German Society for Mucopolysaccharidosis and medical advisor of the Brains for Brain Foundation as well as of several patient associations and medical associations in particular in the East European Countries.

MICHAEL BECK



Prof. Emeritus at the Institute of Human Genetics, University of Mainz in Germany since 2014. He completed training in pediatrics at the Children's Hospital and in genetics at the Institute for Human Genetics, both at the University of Frankfurt/Main in Germany. In addition, he received fellowships from the Biochemical Institute of the University of Münster in Germany and at the University of Houston in Texas. He has extensive expertise and work experience: Paediatrician at the Children's Hospital University of Mainz (1980-2013); Senior consultant at the Children's Hospital University of Mainz and Head of the Biochemical Laboratory at the Children's Hospital University of Mainz (1993-2013); Professorship in Paediatrics. Subject of the Habilitation: Proteoglycan Metabolism in Skeletal Dysplasias (1993) and Head of the Department for Lysosomal Storage Disorders at the Children's Hospital University of Mainz (Villa Metabolica) (2002-2013).

Further relative activities include :

Training in Biochemistry at the Institute of Biochemistry of the University of Münster (Head: Prof. Dr. K. von Figura). Subject: Proteoglycan metabolism in Genetic Diseases in 1983; Research on Metabolism of Chondrocytes in Genetic Skeletal Dysplasias (University of Texas, Houston TX) in 1987; Organization of the 3rd International Symposium on Mucopolysaccharidoses and Related Diseases (in Essen) in 1993; Organization of the 8th International Symposium on Mucopolysaccharidoses and Related Diseases (in Mainz) in 2004. From 2002 to 2013 he was Principal Investigator in Clinical Trials (Enzyme Replacement Therapy in Fabry disease, MPS I, MPS II, MPS VI, MPS IV and other disorders. In the same period he also performed a Study on Natural History of Mannosidosis, (Project of the 6th European Frame Programme) and a Study on Enzyme Replacement Therapy in Mannosidosis (Project of the 7th European Frame Programme). He has vast and extensive experience in teaching and over 100 presentations were given at various scientific international meetings. Most lectures concerned the clinical manifestation of lysosomal storage disorders. Among others (invited) plenary lectures were given at the following meetings: American Society of Human Genetics (ASHG), Society for the Study on Inborn Errors of Metabolism (SSIEM), European Congress of Human Genetics, European Study Group on Lysosomal Diseases (ESGLD)



He was an invited speaker at the University of Tokyo (Children's Hospital), at the University of Toronto (Children's Hospital), at the University of Sydney (Children's Hospital), University of London (Hospital Great Ormond Street).

He is a member of the Deutsche Gesellschaft für Kinderheilkunde (German Society of Pediatrics), the Deutsche Gesellschaft für Humangenetik (German Society of Human Genetics), SSIEM (Society for the Study of Inborn Errors of Metabolism), ESPR (European Society for Paediatric Research), the ESGLD (European Study Group on Lysosomal Diseases) and the American Society of Human Genetics (ASHG). He is the author of more than 300 scientific papers, mostly in peer-reviewed international journals.

WOLFGANG KAMIN



Head of the Children's Hospital at the Lutheran Hospital in Hamm, Germany, since 2009 Professor for Biomedical Engineering at the University of Hamm-Lippstadt, Teaching assistant Professor at the Johannes-Gutenberg-University Mainz Board certified for Pediatrics, Pediatric Gastroenterology, and Pediatric Pneumology/Allergy, Neonatology and Pediatric Intensive Care Further main interest and specialized in Environmental Medicine, Emergency Medicine, Cystic fibrosis and Family Practice.

In 1995, Prof. Kamin established the Cystic Fibrosis Center in Mainz, Rhineland-Palatinate, Germany, including a lung transplant unit and a nationwide recognized educational centre for pediatric allergy, environmental medicine and cystic fibrosis. For ten years (1998-2008) he was chair of the quality circle Pediatric Asthma and Cystic Fibrosis in Rhineland-Palatinate, Germany. He still is a board member of the Medical Association of the district Rhine-Hessen, Germany, and corporate officer of WAPPA (Westdeutsche Arbeitsgemeinschaft für pädiatrische Pneumologie und Allergologie), an association of pediatricians specialized on allergy and pulmonary medicine. In 1986-1988, Prof. Wolfgang received an internship at the University of California San Francisco. He finished his pediatric basic education at the University of Illinois and Cook County Hospital, Chicago in the USA. He was formerly a Paediatrician at the Johannes-Gutenberg University Mainz in Germany from 1990- 2008.

Prof. Kamin acts as a reviewer for different scientific journals, e.g. Pediatrics, European Journal of Pediatrics, Journal of Cystic Fibrosis, European Respiratory Journal, Clinical Intensive Care, Pediatric Pulmonology, Current Medical Research & Opinion, and is a member of the Hunter Syndrome European Expert Council.

The research of Prof. Kamin comprises different aspects of pediatric pulmonary medicine and allergy with focus on the special needs of cystic fibrosis patients, for example when exposed to high altitudes. Development of pediatric bronchoscopes and improvement of inhalation therapy in childhood (e.g. optimizing lung deposition, compatibility of drug admixtures in nebulizers) are part of his main interests, too. According to this, he gave presentations at numerous conferences all over the world and is author and co-author of many publications in peer-reviewed journals. Recently he initiated a clinical trial concerning liver involvement during acute respiratory tract infections in children and adolescents.



ANNEROSE KEILMANN



Prof. Dr. med. Annerose Keilmann, University training: 1979-1985 Medicine in Homburg and Freiburg, Germany .
 Doctorate about electrophysiology of the heart postdoctoral lecturing qualification: about deprivation of the auditory pathways working 1986-96 ENT department Mannheim, 1996-2015 Department for Communication Disorders Universität Mainz since 2015 Head of the Voice Care Center Bad Rappenau
 Professional specialization: ENT, Phoniatics and Pedaudiology.

RENZO MANARA



Neuroradiologist since 2001.
 Associate Professor c/o the Department of Medicine and Surgery, University of Salerno, Italy.
 Teacher in charge of the degree course in Audiological Diagnosis And Health Management at the University of Padova, Italy.
 He has been involved in numerous national and international studies on stroke, cancer, sclerosis, multiple, dementia (IST, ECASS 3, SCITEA, SIRIA, BENEFIT, SENTINEL, COGIMUS, VITA etc.).
 Responsible of the study "MR Angiography Study in Acromegaly" at the University of Padova.

Component of CNS Working Group of FOS (Fabry Outcome Survey).
 Neuro-radiologist consultant of the CNS Working Group of the HOS (Hunter Outcome Survey).
 He gave presentations at numerous conferences in Europe and is author and co-author of many publications in peer-reviewed journals.



MANFRED SCHWARTZ



Manfred Schwartz is a neurosurgeon, specialized on pediatric neurosurgery. He has been working at the Department of Neurosurgery of the University Medical Center of the University of Mainz for more than 30 years. Since 2010 he is working at the Helios Dr Horst Schmidt Kliniken Wiesbaden. Dr Schwartz is specialized on surgical treatments in inborn malformations of the CNS, in particular Spina bifida, Mucopolysaccharidoses and brain tumors. He is supporting also other hospitals with his surgical expertise. As an expert for rare CNS malformations, he is asked as a counsellor from worldwide. He is an active member of several patients associations. In the field of MPS he performed more than 150 decompression surgeries of the cranioservical junction and also published about decompression surgery in MS VI and IV.

ANDREA BORGIO



Andrea Borgo is a Orthopaedic Surgeon. He works as a Staff Physician at the Complex Orthopaedics and Traumatology Unit of the University general Hospital of Padova.
 At the complex unit where Dr.Borgio works, surgical procedures are performed both in adults and children and consequently his activity is divided between these two groups. He personally follows all children and adults affected by mucopolysaccharidoses and performs surgical procedures when needed., from axial correction of the limbs in the youngest to arthroplasty in the older ones.

Since the end of the '90s, Padua progressively become a national reference centre for all enzyme replacement therapies for rare diseases, in particular for MPS. Dr. Borgo, involved from the very beginning, joined the MPS multidisciplinary team as an Orthopaedic Consultant. His clinical and surgical experience was initially limited to the paediatric patients, however, when these patients grew up and become adults, they started to ask for possible solutions for their new orthopaedic problems. In this way, dr. Borgo's clinical and surgical experience extended from treating children only to treating both children and adults.
 Dr. Borgo intensively collaborates with the Italian MPS family association and he is part of some international working groups of MPS. He is an active member of the Italian Paediatric Orthopaedic Society (SITOP) as well as of the European Paediatric orthopaedic Society (EPOS).



CHRISTOPH KAMPMANN



Univ.-Prof. Dr. med. Christoph Kampmann MD, PhD.
 Since 1996 working on the field of lysosomal storage diseases (LSDs) and their impact on the heart and cardiovascular system (PhD thesis about M. Fabry and the heart in 2003). He also completed a Degree in GUCH (grown up congenital heart disease in 2009 further extending his expertise in heart disease management.
 He collected experience in more than 700 patients with different LSDs. So far more than 80 publications in peer reviewed journals about LSDs and the heart. Multiple international cooperations and publications with different LSD centers and basic science centers.

Since 1998 head of department of congenital heart disease and inherited cardiomyopathies at the children's university hospital Mainz, since 2005 full university professorship for Pediatric Cardiology and since 2013 re-announced life time university professorship for congenital heart diseases.

JOCHEN WAHL



He studied mathematics and physics at the University of Heidelberg (1981-1983) and medicine at the University of Heidelberg (1983-1990).
 He has a vast professional experience:
 1991 – 1996 Resident in department of ophthalmology, University of Heidelberg-Section Orthoptics, and Disturbances of Motility (Director: Ellen Kraus-Mackiw, MD).
 1996 – 2000 Resident in Department of Ophthalmology, University of Mainz (Director: Norbert Pfeiffer, MD).
 2001 – 2015 Consultant in Ophthalmology, in department of ophthalmology, University of Mainz (Director: Norbert Pfeiffer, MD).

Since 2015 Head of section Glaucoma and Corneal Surgery in HELIOS Dr. Horst Schmidt Kliniken, Wiesbaden (Director Stefan Dithmar, MD).



ALEXIA ZIMMER



Alexia was born in 1981 in Goch, Germany.
 She was diagnosed by Prof. Dr. Beck with a mild form of MPS VI when she was six years old.
 Alexia was able to attend normal schools throughout her education.
 She now lives in Königstein and works full time as a teacher for children with special needs and her weekly EET and physical therapy does not interface with her work schedule.
 Her hobbies include reading, cooking, working out and long drives in her convertible.

FLORIAN LAGLER



Florian B. Lagler MD, is a metabolic paediatrician and a clinical / translational researcher in the field of lysosomal storage diseases and other inborn errors of metabolism (IEM).
 He was trained in paediatrics and paediatric metabolic medicine (1999-2004 Dr. von Hauner Children's Hospital, Munich) and basic and clinical pharmacology (2004-2011, Innsbruck Medical University). He is Chair of the Research Institute for Inborn Errors of Metabolism at Paracelsus Medical University and CEO of the Clinical Research Center Salzburg. He serves as an advisor for the Austrian Agency for Health and Food Safety (AGES), as a drug commissioner in the German Society for Children and Youth Medicine and as editor of Monatsschrift Kinderheilkunde, the Organ of German and Austrian Society of Paediatrics and Adolescent Medicine.



NOTES

TALK ABSTRACTS

CLASSIFICATION AND PATHOPHYSIOLOGY OF MPS

CHRISTINA LAMPE

Centre for Rare Disease at the Helios Dr. Horst Schmidt Kliniken (HSK) in Wiesbaden, Germany

Mucopolysaccharidosis (MPS) are a heterogeneous family of inborn metabolic conditions caused by the deficiency of one of the enzymes responsible for the degradation of glycosaminoglycans (GAGs). There are 11 known enzyme deficiencies that cause seven distinct types of MPS: namely I, II, III, IV, VI, VII and IX. Although it is accepted that MPS is a progressive disorder and the various types share many clinical features, the presenting symptoms vary depending on the enzyme affected and severity of the disease. The extent of symptoms and rate of progression will also vary between individuals affected by a specific type. In particular, there are attenuated or slow-progressing forms that are less well known and constitute a diagnostic challenge since they develop slowly and insidiously and are often not diagnosed until the patient is an adolescent or an adult. Early and accurate diagnosis of MPS is critical to the provision of appropriate supportive care and, when available, disease-specific treatment. It is therefore crucial to promptly refer all patients with suspected MPS to a geneticist or metabolic specialist.



GENETICS AND EPIDEMIOLOGY OF MPS

MICHAEL BECK

Institute of Human Genetics at the University of Mainz, Germany

The overall incidence of the MPS disorders is difficult to estimate because of the scarcity of population-based studies. From epidemiologic data collected from different countries the incidence of all mucopolysaccharidoses has been estimated to be about 4 of 100.000 newborns. In Northern Europe MPS III A is the most common MPS disorder, whereby MPS VI and MPS IVA are relatively frequent in Turkey. There exist clusters in which a high incidence of a mucopolysaccharidosis have been found: In an area of Northeast Brazil, for example, a large number of MPS VI patients has been detected that can be explained by a founder effect. In Ireland a high incidence of MPS IVA has been described. Preliminary results of newborn screening projects provide an indication that the mucopolysaccharidoses are much more common than it was calculated from epidemiological investigations. In a pilot study, performed in the US state Missouri, blood samples of 43 701 newborns were screened for four lysosomal storage disorders. In this study, three MPS I patients were detected, giving an incidence of 1:14 567.

With one exception, all mucopolysaccharidoses are inherited in an autosomal-recessive manner, only MPS II (Hunter disease) is an X-linked disorder. In all MPS types numerous mutations (missense mutations, nonsense mutations, small deletions or insertions, large deletions and rearrangements) have been identified. Although there is no strong genotyp-phenotype correlation, there exist some mutations that are almost always associated with a severe phenotype: In MPS IH (Hurler disease) the nonsense mutations Q70X and W402X are very common. Patients with one of these mutations are suitable for the treatment with drugs that are able to suppress premature stop codons and to continue translation, leading to partial restoration of enzymatic function. A first clinical trial with one of these drugs has been initiated recently. Generally, carriers of the X-linked MPS II do not exhibit any clinical signs. There have been described, however, a few female MPS II patients who show clinical manifestations of variable degree. As an explanation for this observation different mechanisms have been discovered; these are either structural anomalies of the X-chromosome, an unequal X-inactivation or a homozygous status in a child of a consanguineous couple. In each female Hunter patient, thorough investigations (mutation analysis, chromosomal analysis and assessment of the degree of X-inactivation) are mandatory in order to clarify the cause of the clinical manifestation.

The new technologies such as next generation sequencing, whole exome sequencing and even whole genome sequencing allow fast and reliable gene analysis; however, for the evaluation and interpretation of the huge amount of data that are delivered by these methods, a close cooperation is required between molecular biologists and physicians, who have large experience in clinical genetics.



RESPIRATORY PROBLEMS IN MPS

WOLFGANG KAMIN

Lutheran Hospital in Hamm, Germany

Respiratory problems are frequently encountered by patients with Hunter syndrome and contribute to the premature mortality seen in the disease. Progressive deposition of glycosaminoglycans in the soft tissue of the throat and trachea is thought to be responsible for the airway dysfunction and obstruction which characterize the syndrome. Other physical characteristics, including abnormalities in the shape and structure of the ribs, abdominal organ enlargement, short neck and immobile jaw, further contribute to the respiratory problems. New measurement systems specifically tailored to paediatric patients now allow clinicians to follow the progressive deterioration of lung function, which was previously challenging in this population. Sleep apnoea is another common feature of Hunter syndrome, which can lead to a reduction in oxygen saturation of the blood and severely disrupts sleep. In our clinic, continuous positive airway pressure, in which inspired air at elevated pressure is delivered through a specially designed mask, has proved to be effective for reducing sleep apnoea in patients with Hunter syndrome. As a consequence of the anatomical and pathological changes in the upper airways of patients with Hunter syndrome, general anaesthesia – especially intubation – is a difficult and potentially high-risk procedure. Consequently, such procedures should be performed by an anaesthetist – ideally accompanied by a paediatric pneumologist/intensivist – with experience in managing patients with Hunter syndrome.



ANESTHESIOLOGY PROBLEMS: DISCUSSION OF MPS CASES

CHRISTINA LAMPE

Centre for Rare Disease at the Helios Dr. Horst Schmidt Kliniken Wiesbaden, Germany

The mucopolysaccharidoses (MPS) are inherited lysosomal storage diseases associated with accumulation of glycosaminoglycans (GAGs) in tissues and organs responsible of a progressively worsening organ dysfunction that eventually leads to a decreased lifespan.

Most MPS patients require anaesthesia for multiple surgical interventions to help manage the disease. Unfortunately, surgery is often associated with a high mortality rate since the high prevalence of airway obstruction and restrictive pulmonary disease in combination with cardiovascular manifestations with accompanying difficulty in ventilation and oxygenation pose a high anaesthetic risk to these patients. Here we will present a detailed overview and discussion about main anaesthetic risk factors in MPS, the importance of undertaking a careful assessment of the patient risk/benefit ratio associated to the procedure in order to properly consider every single case individually. Related anaesthetic management, including emergency airway issues will also be illustrated.



THE EAR NOSE AND THROAT IN MPS

ANNEROSE KEILMANN

Voice Care Center Bad Rappenau, Germany

Abnormalities of the upper respiratory tract are common in patients with MPS and include enlargement of the lips, tongue and mucosa of the vallecula, mucosa of the laryngeal vestibule, false and true vocal folds, and mucosa of the posterior region of the larynx. Patients often suffer from inflammations and often ENT surgery (as adenoidectomy and tonsillectomy) is helpful. Because of the narrowing of the upper airways some patients have a tracheostomy.

Furthermore most patient develop hearing disorders, during childhood mostly caused by otitis media with effusion, later by granulations in the middle ear and depending on the subtype of MPS although sensori-neural hearing losses. Children often get ventilation tubes, adult patients need often hearing aids.



NEUROLOGY OF MPS

MAURIZIO SCARPA

*Centre for Rare Disease at the Helios Horst Schmidt Klinik (HSK) in Wiesbaden, Germany
InNerMeD Project Coordinator and President of the Brains for Brain Foundation, Italy*

The mucopolysaccharidoses (MPS) are a group of progressive multisystemic diseases having in common an excessive accumulation of mucopolysaccharides secondary to deficiencies in specific enzymes. Accumulation begins in infancy and progressively worsens, often affecting several organs, including the central nervous system (CNS). Affected neurons may die through apoptosis or necrosis, although neuronal loss usually does not occur before advanced stages of the disease. CNS pathology typically causes mental retardation, progressive neurodegeneration and premature death. In particular, depending on the mucopolysaccharidoses subtype, affected individuals may have normal intellect or may be profoundly impaired, may experience developmental delay, or may have severe behavioral problems. Although MPSs share many clinical features, a wide heterogeneity in their severity is present also within the same phenotype, with a wide spectrum of clinical forms ranging from attenuated (slowly progressing) to very severe (rapidly progressing) forms of the disease. In the last years knowledge about the pathology and clinical course of MPS has been rapidly increased and enormous progress has been made in the treatment of many MPS types. Early diagnosis and early treatment are crucially helpful to the patients. Many of the available treatments can in fact result efficacious only if they are administered before neurodegeneration becomes irreversible. Unfortunately diagnosis of MPS is still often challenge especially for patients who have more slowly progressive disease phenotypes.



NEUROIMAGING AND MPS

RENZO MANARA

University of Salerno, Italy

The mucopolysaccharidoses (MPSs) comprise a group of disorders characterized by progressive lysosomal accumulation of glycosaminoglycans (GAGs). GAGs can accumulate in the growing cartilage resulting in dens dysplasia, atlanto-axial instability, and subsequent odontoid fibrocartilaginous tissue deposition with upper cervical stenosis. Compressive cervical myelopathy is a well-known life-threatening complication in MPS patients. In MPS patients a periodical neurological examination (brain and cervical MRI imaging) is extremely important for preventing major neurological complications.



NEUROSURGERY AND MPS

MANFRED SCHWARTZ

Helios Dr Horst Schmidt Kliniken, Wiesbaden, Germany

Mucopolysaccharidoses (MPSs) represent a group of rare hereditary disorders characterized by multi-system involvement due to intralysosomal accumulation of glycosaminoglycans (GAGs). Among various tissues, both the central and peripheral nervous system are affected in almost all types of the disease. Skeletal deformities affecting the spine are in fact common hallmarks in many patients with MPSs and are often associated with cord compression and myelopathy, leading to major morbidity and mortality. Intervention is often required. Decompressive procedures have shown significant improvement in neurological function in the majority of patients without spinal instability. Due to the complexity and rarity of these disorders, as well as high risk of anesthetic and surgical complications, individuals with this disease should be monitored and treated at a facility with an expertise in treating patients with MPSs.



ORTHOPEDIC PROBLEMS IN MPS

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Orthopaedic aspects of MPS depend on the severity of the disease. Vertebral bodies flattened, C2 odontoid hypoplasia and a thoracolumbar kyphosis are present. Chest wall presents oar-shaped ribs and short clavicles. Hands and feet present bullet-shaped phalanges. Distal radius is often curved. Pelvis X-rays demonstrate flared iliac wings with a small pelvis with an acetabulum poorly developed and a lack of ossification of its superolateral portion, dysplasia of the femoral head and valgus deformity of the proximal femur. Lower legs are characterized by valgus deformities of the knee and ankle. An ossification delay is common. Disproportional short stature with the trunk proportionally shorter than the limbs is common. GAGs soft tissues storage lead to stiffness and contractures and to an early onset of carpal tunnel syndrome and trigger digit.



CARDIOLOGY AND MPS

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The mucopolysaccharidoses (MPSs) are inherited lysosomal storage disorders caused by the absence of functional enzymes that contribute to the degradation of glycosaminoglycans (GAGs). The progressive systemic deposition of GAGs results in multi-organ system dysfunction that varies with the particular GAG deposited and the specific enzyme mutation(s) present. Cardiac involvement has been reported in all MPS syndromes and is a common and early feature, particularly for those with MPS I, II, and VI. Cardiac valve thickening, dysfunction (more severe for left-sided than for right-sided valves), and hypertrophy are commonly present; conduction abnormalities, coronary artery and other vascular involvement may also occur. Cardiac disease emerges silently and contributes significantly to early mortality. The clinical examination of individuals with MPS is often difficult due to physical and, sometimes, intellectual patient limitations. The absence of precordial murmurs does not exclude the presence of cardiac disease. Echocardiography and electrocardiography are key diagnostic techniques for evaluation of valves, ventricular dimensions and function, which are recommended on a regular basis. The optimal technique for evaluation of coronary artery involvement remains unsettled. Standard medical and surgical techniques can be modified for MPS patients, and systemic therapies such as hematopoietic stem cell transplantation and enzyme replacement therapy (ERT) may alter overall disease progression with regression of ventricular hypertrophy and maintenance of ventricular function. Cardiac valve disease is usually unresponsive or, at best, stabilized, although ERT within the first few months of life may prevent valve involvement, a fact that emphasizes the importance of early diagnosis and treatment in MPS.

Abstract from "Braunlin EA, Harmatz PR, Scarpa M, Furlanetto B, Kampmann C, Loehr JP, Ponder KP, Roberts WC, Rosenfeld HM, Giugliani R. Cardiac disease in patients with mucopolysaccharidosis: presentation, diagnosis and management. *J Inherit Metab Dis.* 2011 Dec;34(6):1183-97".



OPHTHALMOLOGICAL PROBLEMS IN MPS: GLAUCOMA AND CORNEAL SURGERY

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In MPS ocular involvement occurs early. Typical manifestation in the eye include opacification of the cornea, increase in ocular pressure with ocular hypertension or glaucoma. Additionally, retinal degeneration, swelling of the optical nerve head and atrophy of the optic nerve are seen. Due to shallow orbits, exophthalmos is frequent. Amblyopia and large refractive errors emerge.

Functionally this can lead to blurred vision and visual field constriction, photosensitivity and night blindness.

The improvement and introduction of new tools such as OCT and UBM have facilitated diagnostics. New surgical techniques such as deep anterior keratoplasty and stem cell transplantation have also been established and can improve the eye sight up to a reasonable and servicable function for the patients.



LIVING WITH MPS, A PERSONAL EXPERIENCE

ALEXIA ZIMMER

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Each type of mucopolysaccharidosis (MPS) differs in clinical presentation and has varying degrees of severity. Here will be presented the “Impact of growing older with MPS on the patient’s daily life: the patient’s perspective”. A description of the influence of a rare condition on patient’s daily life, a direct personal experience about the way in which Alexia experiences her disease, her health and her functional abilities. An interactive and emotional discussion that will represent a great opportunity for establishing and reinforcing the doctor–patient relationship.



ERT, PRINCIPLE AND PROCEDURES

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Enzyme replacement therapies (ERT) are now becoming available for a growing number of MPS. ERT can substantially improve the clinical course of the diseases, yet there is a potential for adverse, primarily infusion-related, reactions. Infusion reactions can present with a broad spectrum of symptoms and levels of severity from mild unspecific signs to life threatening anaphylactic reactions. Additionally some features of the disease like cardiac involvement, altered anatomy of the airways, cranio-cervical instability put the MPS patients at a high risk for adverse outcomes in such emergency situations.

Thus, adequate technical knowledge about the preparation and administration of ERT and awareness of the specific needs of MPS patients is a prerequisite for all medical and paramedical professionals providing ERT. An appropriate clinical environment and safe routine procedures can reduce the probability for severe infusion reactions. Moreover, the ability to apply the needed knowledge even under the challenging circumstances of an emergency is the key to patient safety. Deliberate practice is the training method of choice for the acquisition and improvement of these skills.

The participants will have the opportunity to provide ERT to a simulated patient, recognize the signs of infusion-related reactions and perform the indicated emergency measures. Within an interactive debriefing the performance will be reflected and improvement strategies will be elaborated. Thus, the participants will assess and improve their preparedness for providing ERT in a safe way and mastering infusion-related reactions.



ERT SAFETY

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The advent of enzyme replacement therapy (ERT) has significantly changed the disease course of several LSDs improving patients clinical outcomes, quality of life and survival. ERT is not curative, it has to be continued life long, and to be safe and therapeutically useful ERT products must be intravenously infused, usually every other week, according to specifically adequate dosages determined by patient body weight. Related benefit includes improved walking ability and improved respiration. ERT is now commercially available, both in the United States and Europe, for treating peripheral manifestations of several LSDs, including MPS. Up to now recombinant i.v. ERT is available for MPS I, II, IV and VI. Clinical safety and efficacy of ERT have been extensively assessed by several clinical studies clearly showing its positive effects on several non-neurological symptoms. Unfortunately, ERT does not cross the blood brain barrier (BBB) and therefore it is still not able to effectively reach the central nervous system. Efforts are therefore directed toward the development of new strategies to enhance drug delivery across the BBB. The availability of a sufficient quantity of stable, safe and non-immunogenic exogenous enzyme constitutes a crucial prerequisite for effective ERT. To accomplish all these requirements, the nature and function of the enzyme inside the cells and pathophysiological events in the disease must be carefully considered.



ERT, IMMUNOLOGY AND MANAGEMENT OF SIDE EFFECTS

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ERT represents the most important advancement and a major breakthrough in the treatment of many LSDs. Its basic principle consists in replacing the specific defective enzyme in LSDs patients through periodic intravenous infusions of the functional enzyme produced and purified on large scale from different sources with recombinant DNA techniques. Still, clinical experience with ERT has revealed that some related infusion reactions may occur in recipients. Infusion reactions are generally mild and include brief, insignificant decreases or increases in heart rate, blood pressure, or respiratory rate, cutaneous reactions (pruritis; rash; erythema, urticarial) and headache. Mild reactions can usually be managed by slowing the infusion rate for several treatments and then slowly returning to the prior rate. Prevention of primary manifestation is a very important task since these infusion-associated adverse events such as immune reactions against the infused enzyme can represent obstacles to successful ERT.

NOTES

This programme is in collaboration with



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