BIMDG Annual Symposium 2021

Thursday 24th June 2021

Virtual Conference

BIMDG

British Inherited Metabolic Diseases Group

@BIMDG

The BIMDG would like to thank the following companies for supporting their 2021 annual conference. They have had no input to speakers or presentations.

Aims & Objectives of the Conference

To bring together multi-disciplinary professionals involved in the care of children and adults with rare inherited metabolic diseases. This meeting will provide educational and scientific updates for healthcare professionals in the field of inherited metabolic disease. National and international experts are invited to speak providing an excellent overview.

Individual sub-specialist meetings provide the opportunity for dieticians, clinical scientists, nurses, pharmacists, psychologists & Adult IMD to interact and gain invaluable practical and scientific education. This annual meeting is an excellent opportunity for professionals from around the UK and also international colleagues to network.

Accreditation

This meeting has been approved by the Royal College of Pathologists for **5 CPD credits.**

PROGRAMME

2021 VIRTUAL CONFERENCE – THURSDAY 24TH JUNE 10.00AM – 5.00PM

Royal College of Pathologists (RCPath) CPD accreditation approved
for 5 CPD credits

IMPROVING DIAGNOSIS AND TREATMENT

10.00-10.05 INTRODUCTION

DIETETIC SESSION

Chair : Alison Woodall, Metabolic Dietician, Salford Royal NHS Foundation Trust, Salford

10.05-10.35 **Wolman- immunological and dietetic aspects of management**
Fiona White, Metabolic Dietician and Arunabha Ghosh, Consultant Paediatrician, Willink Unit, Manchester

10.35-11.05 **GA1 results of newborn screening and UK dietary consensus**
Marjorie Dixon, Clinical Lead Dietitian – metabolic medicine, GOSH, London & Mildrid Yeo, Consultant in Paediatric IEM, GOSH, London

11.05-11.35 **The management of complex nutritional needs in MNGIE**
Antje Teubner Associate Specialist, Intestinal Failure Unit, Salford

11.35-11.50 BREAK

ADULT SESSION

Co-Chair : Gisela Wilcox, IMD Consultant, Salford Royal NHS Foundation Trust, Salford & Radha Ramachandran, IMD Consultant, Guy's & St Thomas' Hospital, London

Chosen from abstracts submitted :

11.50-12.05 **Developmental consequences of defective ATG7-mediated autophagy in humans**
Professor Rob Taylor, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne

12.05-12.20 **A case study of a patient with Aicardi-Goutières syndrome presenting as a possible Peroxisomal disorder**
Corey Pritchard, University Hospitals Bristol & Weston

12.20-12.50 **Late-onset MTHFR- a novel disease?**
Fanny Mochel, Consultant Neurologist, Reference Centre for Neurometabolic Diseases, Paris

12.50-13.50 LUNCH

13.50-15.20 MEMBER'S ORAL PAPERS CHOSEN FROM ABSTRACTS
Chair : Radha Ramachandran, IMD Consultant, Guy's & St Thomas' Hospital, London

13.50-14.05 **Social, emotional & behavioural outcomes in children born to women with PKU & their relationship with maternal metabolic control**
Charlotte Ellerton, UCLH ,London

14.06-14.20 **The use of glycerol phenylbutyrate in adult patients with Urea Cycle Disorders - one centre experience**
Faiza Adrees, Salford Royal NHS Foundation Trust, Salford

14.21-14.35 **Sitosterolaemia effectively managed with dietary modification + Ezetimibe**
Katie Rawlins, GSTT, London

14.36-14.50 **Results of general newborn screening for Isovaleric Acidaemia in the North-West of England**
Bernd Schwahn, Willink Unit, Manchester

14.51–15.05 **Adult-onset generalised dystonia as the main phenotypic feature of alpha-methylacyl-CoA racemase deficiency**
Francesca Magrinelli, UCLH, London

15.06-15.20 **SRD5A3-CDG: Emerging phenotypic features apart from the eye involvement**
Nazreen Banu Kamarus Jaman, GOSH, London

15.20-15.35 Student summer projects summary from 2019 awards :

An in vitro proof of principle study to test the efficacy of translational read-through therapy for mitochondrial disorders
Melissa Kuo, now a 5th year Medical Student at UCL London

Natural protein and phenylalanine tolerance and metabolic control in patients with hereditary tyrosinaemia type I (HTI).
Ozlem Yilmaz, now a PhD Dietetic Student in Turkey

15.35-15.50 BREAK

SCIENTIST SESSION

Co-Chair : Teresa Wu, & Heather Church, Willink Biochemical Genetics Unit, Manchester University NHS Foundation Trust

15.50-16.20 **Laboratory development of clinically useful antibody monitoring in Enzyme Replacement Therapy**
Katherine Brammeier, Senior Biomedical Scientist/Simon Jones, Consultant Paediatrician, Willink Unit, Manchester

16.20-16.50 **How to improve IMD monitoring with patient collected samples during COVID-19 pandemic**
Helena Kemp, Chemical Pathology Consultant, Bristol

16.50-17.00 BREAK

17.00 AGM – Members only

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All day

In a pooled analysis of four studies involving short and long term treatment of patients 6 years and above:

- Mean ammonia and glutamine levels were shown to be significantly lower ($p<0.05$) in the pooled analysis on Ravicti treatment compared to Sodium Phenylbutyrate (NaPBA)
- Patients switched from NaPBA treatment to long term Ravicti treatment showed significant improvements in executive function (patients aged 6- 17 years)
- Long term treatment with Ravicti has been associated with fewer decompensations vs NaPBA[1]

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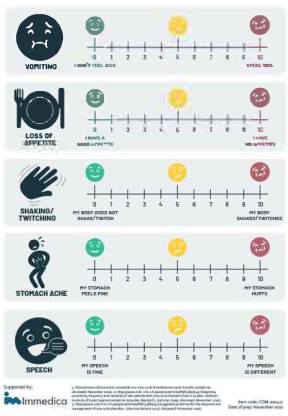

1

1 – For Patients
An informative guide for patients diagnosed with a Urea Cycle Disorder.

2

2 – For HCP's
Dosing guide that helps physicians experienced in the management of UCDs establish the correct Ravicti dose for patients.

3

3- For Patients
A tool to facilitate a discussion between patient and HCP's about the symptoms patients are experiencing as well as their intensity and frequency.

4

4 – For Patients
Support booklet for patients that have been prescribed Ravicti.

5

5- For HCP's
A promotional slide deck explaining the mechanism of action of Ravicti and its effects on ammonia control.

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List Price: Ravicti 1.1 g/ml oral liquid. £161.00 per bottle excluding VAT. EIRE List Price: Available on request.
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This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information.
Adverse reactions are to be reported according to national local regulations. Reporting forms and information can be found for UK at www.mhra.gov.uk/yellowcard and for Ireland at www.hpra.ie
Adverse reactions can also be reported to Immedica Pharma UK Ltd by email at safety@immedica.com

References: 1. Diaz GA et al. Hepatology. 2013;57(6):2171-2179
COM-000800, Date of preparation: April 2021

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SPEAKER BIOGRAPHIES & ABSTRACTS

DIETETIC SESSION

THURSDAY 24TH JUNE

Life is a health journey

with its ups and downs, and its challenges. These can be big or small, lifelong or temporary. Everyone, from childhood to old age, faces health challenges and needs, wherever they are.

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MAT-GB-2100466(v1.0)
Date of Preparation February 2021

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PERSONAL BACKGROUND

Alison Woodall
Specialist Metabolic Dietitian

Mark Holland Metabolic Unit
Salford Royal NHS Foundation Trust
Salford Care Organisation
Part of the Northern Care Alliance NHS Group

Alison is currently a metabolic dietitian and has been working at the Salford Royal Hospital as a specialist metabolic dietitian for nearly three years. There are a wide variety of metabolic patients at Salford and although she primarily sees the general metabolic patients, she has seen some of the Lysosomal Storage Disease patients as well including some of the patients with Fabry Disease. The reason for seeing these patients was to try and optimise management of gut symptoms with diet.

Prior to working at Salford Alison has had a number of other dietetic roles including working as an Upper GI dietitian and as a gastro dietitian. She has also worked as a senior lecturer training future dietitians.

She has a PhD and worked in labs for several years before becoming a dietitian. Alison then decided to change to a dietetic career due to her interest in nutrition and dietetics.

PERSONAL BACKGROUNDS

Arunabha Ghosh, Paediatric Metabolic Consultant, Willink Biochemical Genetics Unit, St Mary's Hospital, Manchester, UK

Arunabha Ghosh has been a consultant in paediatric metabolic medicine at the Willink Unit in Manchester since 2019.

Prior to this, he completed his PhD at the University of Manchester, during which time he undertook investigator-led clinical trials of immune tolerance induction and substrate reduction therapy in mucopolysaccharidoses.

Having worked on the clinical trials of enzyme therapy for infantile onset lysosomal acid lipase deficiency (Wolman disease), and worked with this cohort clinically since, he has developed a particular research interest in this condition.

Fiona White, Lead Specialist Metabolic Dietitian, Willink Biochemical Genetics Unit, St Mary's Hospital, Manchester, UK

Fiona White is Clinical Lead specialist metabolic dietitian at the Willink Unit in Manchester with over 25 years experience in the speciality.

As part of the clinical team looking after children with infantile onset lysosomal acid lipase deficiency (Wolman disease) from the initial clinical trials of enzyme therapy onwards has developed a keen interest in their nutritional care and has been instrumental in the evolving of nutritional management guidelines for this population.

Abstract

Wolman disease: immunology, nutrition, and moving beyond ERT

Collaborators:
Jane Potter, Clinical Research Fellow, Department of Blood and Marrow Transplantation, Royal Manchester Children's Hospital, Manchester, UK
Gemma Petts, Paediatric Histopathologist, Department of Paediatric Histopathology, Royal Manchester Children's Hospital, Manchester, UK
Rob Wynn, Consultant Haematologist, Department of Blood and Marrow Transplantation, Royal Manchester Children's Hospital, Manchester, UK
Stephen Hughes, Consultant Paediatric Immunologist, Royal Manchester Children's Hospital, Manchester, UK
Anu Goenka, Clinical Lecturer, School of Cellular and Molecular Medicine, University of Bristol, Bristol, UK
Joanne Hughes, Paediatric Metabolic Consultant, National Centre for Inherited Metabolic Disorders, Temple Street, Dublin, Ireland
Jane Roberts, Clinical Nurse Specialist, Willink Biochemical Genetics Unit, St Mary's Hospital, Manchester, UK
Simon Jones, Paediatric Metabolic Consultant, Willink Biochemical Genetics Unit, St Mary's Hospital, Manchester, UK

Background:
Infantile onset lysosomal acid lipase (LAL) deficiency, or Wolman disease (WD), is a rare inherited lysosomal disorder characterised by severe faltering growth and rapidly progressive liver disease, and is invariably fatal in infancy if untreated. The gastrointestinal and hepatic manifestations of this condition are well described, and clinical trials of enzyme replacement therapy (ERT) with sebelipase alfa, together with nutritional management including dietary substrate reduction, have shown a clear survival benefit, Here we describe the immunological aspects of the disease, considering both the primary immune defects observed in WD, as well as the effects of immunological response to ERT. The latter has led to a cohort of individuals with WD in Manchester being treated with HSCT as part of a multimodal therapeutic strategy (nutritional therapy, ERT, and HSCT) (1). We describe their management and outcomes, focussing on the nutritional aspects of management and improvements in gastrointestinal manifestations.

Methods:
Characterisation of primary immune defects was done as per clinical need and involved measurements of immunoglobulin concentrations, T and B cell subsets, and cytokines. Monocytes isolated from patient peripheral blood mononuclear cells were differentiated into monocyte-derived macrophages for macrophage infection assays and cytokine measurements to assess mycobacterial phagocytosis by WD macrophages. Five individuals in Manchester received multimodal therapy for WD, including specific nutritional therapy, ERT, and HSCT (following a period of ERT). At the start of HSCT process all five had significant gastrointestinal disease; four individuals were managed on amino acid based enteral feeds with minimal fat intake, one with supplementary parenteral nutrition and one case total modified parenteral nutrition . Outcome data was collected as part of a retrospective case note review (1).

Results:
Infants with WD can present with a hyperinflammatory picture, including haemophagocytic lymphohistiocytosis (HLH). They also display immune dysregulation with likely an intrinsic macrophage defect, and potentially both a macrophage and T-cell defect. This may be the underlying cause of abnormal response to BCG vaccination in these individuals. The immune response to enzyme replacement therapy can lead to the generation of high titre anti-drug antibodies that negatively impact the efficacy of ERT. Despite ERT, infants with WD have persisting gastrointestinal disturbance with gastrointestinal biopsies showing marked lipid accumulation despite extreme dietary lipid restriction (<1g/day), with a majority of cases requiring amino acid based enteral feeds and enteral tube feeding to support growth. Severe oral feeding aversion is common. Haematopoietic stem cell transplantation not only abrogates the immune response to ERT, but is also associated with improved outcomes. All surviving infants treated with multimodal therapy have reduced or stopped ERT. Post-HSCT, individuals with WD have both improvements in gastrointestinal tract and hepatic histology, as well as clinical improvements in gastrointestinal tract function with tolerance of intact protein, greater lipid tolerance and improved oral tolerance with reduced reliance on enteral tube feeding. Two of the four survivors, both whom have stopped ERT, are currently tolerating a normal diet with unrestricted lipid intake.

Conclusions:
WD is a complex, multifaceted condition and the natural history of treated individuals with this condition is only recently being described in detail. This includes several immunological aspects thus far not well described in literature. While ERT has been shown to have clear survival benefit in clinical trials, it can be associated with the development of anti-drug antibodies that impact on treatment efficacy and ERT does not appear to treat the gut effectively. We demonstrate that HSCT not only effectively abolishes anti-drug antibodies, but as part of a multimodal therapeutic approach (nutritional therapy, ERT and HSCT), it is associated with additional improvements in overall clinical outcomes and quality of life.

References:

1. Potter, J.E., Petts, G., Ghosh, A., White, F.J.*et al.* Enzyme replacement therapy and hematopoietic stem cell transplant: a new paradigm of treatment in Wolman disease. *Orphanet J Rare Dis* **16,** 235 (2021). https://doi.org/10.1186/s13023-021-01849-7

Correspondence
fiona.white@mft.nhs.uk
arunabha.ghosh@mft.nhs.uk

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PERSONAL BACKGROUND

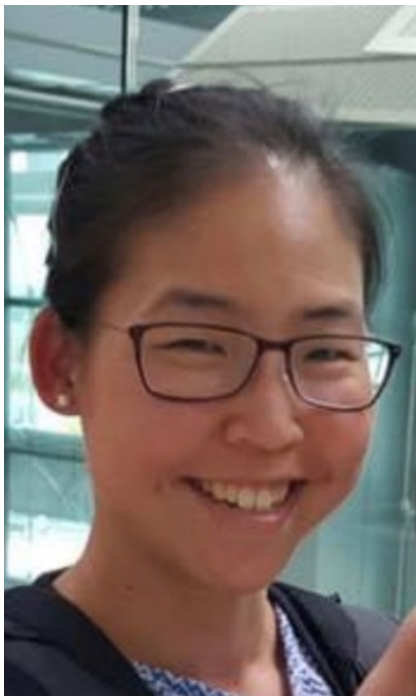
Marjorie Dixon

Clinical Lead Dietitian – metabolic medicine
GOSH, London

Marjorie Dixon qualified as a dietitian in 1981 with a BSc in Nutrition and Dietetics from Robert Gordon's Institute of Technology, Aberdeen, Scotland.

Marjorie joined the Dietetic Department at Great Ormond Street Hospital for Children, London in 1983 as a paediatric dietitian where she is now Principal Paediatric Dietitian of metabolic disorders. Marjorie has specialised in the dietary management of children with inherited metabolic disorders for over 30 years. She is primarily a clinical dietitian but is also involved in teaching (at national and international level) and research work. She is a committee member of SSIEM-Dietitians Group and is an active member of the BIMDG-Dietitians Group,UK. Marjorie is an Honorary Lecturer at the University of Plymouth. She is lead dietitian for the Dietetic management of Inherited Metabolic Disorders module for the MSc in Advanced Professional Practice in Paediatric Dietetics, University of Plymouth. She is co-author of the Dietary Management of Inherited Metabolic Disorders section in Clinical Paediatric Dietetics, 5th edition, 2020.

PERSONAL BACKGROUND



Mildrid Yeo
Consultant in Paediatric IEM, GOSH, London

Dr Yeo first joined the Paediatric metabolic department at Great Ormond Street Hospital for Children, London in 2018 as a grid trainee then as a consultant specialising in children with inherited metabolic disorders. Her interest spans aminoacidopathies and the use of technology and healthcare.

ABSTRACT

Deep phenotyping of Glutaric aciduria type I (GA1) in screened patients
Mildrid Yeo, Paediatric metabolic consultant, Department of Metabolic Medicine, Great Ormond Street Hospital for Children, NHS Trust, London, UK.
Marjorie Dixon, Clinical Lead Dietitian-metabolic medicine, Sarah Cawtherley, Specialist Metabolic Dietitian, Louise Van Dorp, Metabolic Research Dietitian, Dietetics, Great Ormond Street Hospital for Children, NHS Trust, London, UK.
Collaborators: metabolic teams, St Mary's Hospital Manchester University NHS Foundation Trust, Evelina London Children's Hospital, and Birmingham Women's and Children's NHS Foundation Trust.

Background/Aims:
Glutaric aciduria type 1 (GA1) was included in the NHS newborn bloodspot screening (NBS) programme, following the successful pilot project in England during, 2012 to 2014.
This study aims to review a cohort of GA1 patients diagnosed by NBS or sibling screen and describe: (i) their clinical features, dietetic interventions, frequency of use of emergency regimen and growth, (ii) to examine the causal relationship of adherence to medical intervention with neurological outcomes and (iii) compare treatment and outcome to published guidelines and literature.

Methods
Clinical and dietetic data was collected on GA1 patient, diagnosed by NBS, and early or late sibling screening since 2005 from metabolic centres in London (n=2), Manchester and Birmingham. A novel scoring system was developed to assess overall adherence to lysine/protein restricted diet, lysine free protein substitute, emergency regimen (ER) and Levocarnitine.

Results
Medical and dietetic data was available on 35 identified patients. Patients were diagnosed within a median 11 days (range 0-20) with prompt commencement of lysine/protein restricted diet, lysine free protein substitute, Levocarnitine (100mg/kg/day), and GA1 specific ER.

Maintenance diet and ER were based on Boy et al 2017[1], irrespective of age. Thirty-four patients under 6y of age were on a low lysine/protein diet and lysine free protein substitute. Protein foods were measured by scales (n=20), visually (n=2), a combination of both (n=11), or protein foods were not counted (n=2). Thirty-two patients fed orally and by tube (n=3). Frequency of ER use under 6 years of age was available for n=26/35, of those 5 patients had never used ER. In children under 6 years of age the annual frequency of ER use was median 1.8 (range 0-7.2) compared to those over 6 years old (n=9), the median was 0.5 (range 0-1.2).
Overall mean adherence scores (lysine/protein restricted diet, lysine free protein substitute, ER, Levocarnitine), in children under 6 years was 11.2 (SD 1.2), maximum possible score of 12.

No patients had seizures. Gross Motor Function Classification System (GMFCS) scores were 1 (n=31), 3 (n=3), 4 (n=1). One patient has central hypotonia and 4 patients have moderate dystonia (n=2 required single agent therapy for dystonia). All 5 patients had reported poor feeding from birth with a history of 10% weight loss before GA1 was confirmed. Three of the 4 dystonia patients had lower overall adherence scores (<10).

All patients are alive with a median age at last clinic follow up of 3.9 years (range 0.08-15.6).

Conclusion

The clinical outcomes and dietetic treatment from this study will be compared to published guidelines and literature.

Reference

1. Boy N, Muhlhausen C, Maier E M, et al. Proposed recommendations for diagnosing and managing individuals with glutaric aciduria type I: second revision. JIMD. 2017: 40(1):75-101.

E-mail address:
Mildrid.yeo@gosh.nhs.uk
Marjorie.dixon@gosh.nhs.uk

BioMarin develops and commercialises innovative biopharmaceuticals for serious diseases and medical conditions. The company aims to develop first-in-class or best-in-class therapeutics to make a large, meaningful impact on small patient populations. BioMarin provides therapies for patients with rare genetic diseases.

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EU-MPRL-00012 May 2021

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PERSONAL BACKGROUND

Miss Antje Teubner is an Associate Specialist of Intestinal Failure, a position she has held since 2007. Originally from Germany, Miss Teubner graduated in 1994. She undertook her postgraduate training in the UK in surgery and surgical specialties gaining operative and medical experience in the management of critically ill patients.

She has gained extensive experience in the management of patients with acute intestinal failure, as well as patients requiring long term intestinal rehabilitation (including vascular access management, management of high-output fistulae, short bowel and long term HPN complications).

In her role she leads the teaching and supervision of the junior doctors/clinical fellows and has expanded this remit by regularly presenting on national conferences, study days and symposiums as well as lecturing and running workshops on intestinal failure. Her principal goal is to enhance patient care. This is reflected by her numerous peer-reviewed publications and international presentations around quality initiatives in intestinal failure management.

Abstract

‘Management of complex nutritional needs in MNGIE’

Nutritional management is key to the success in any medical practice. This is especially evident in patients with rare diseases. Focusing on case studies this presentation will highlight the challenges in managing patients with MNGIE. It will show how parenteral nutritional support in combination with enteral feeding is applied and how limitations are met. The presentation will illustrate a holistic approach to the management of these patients.

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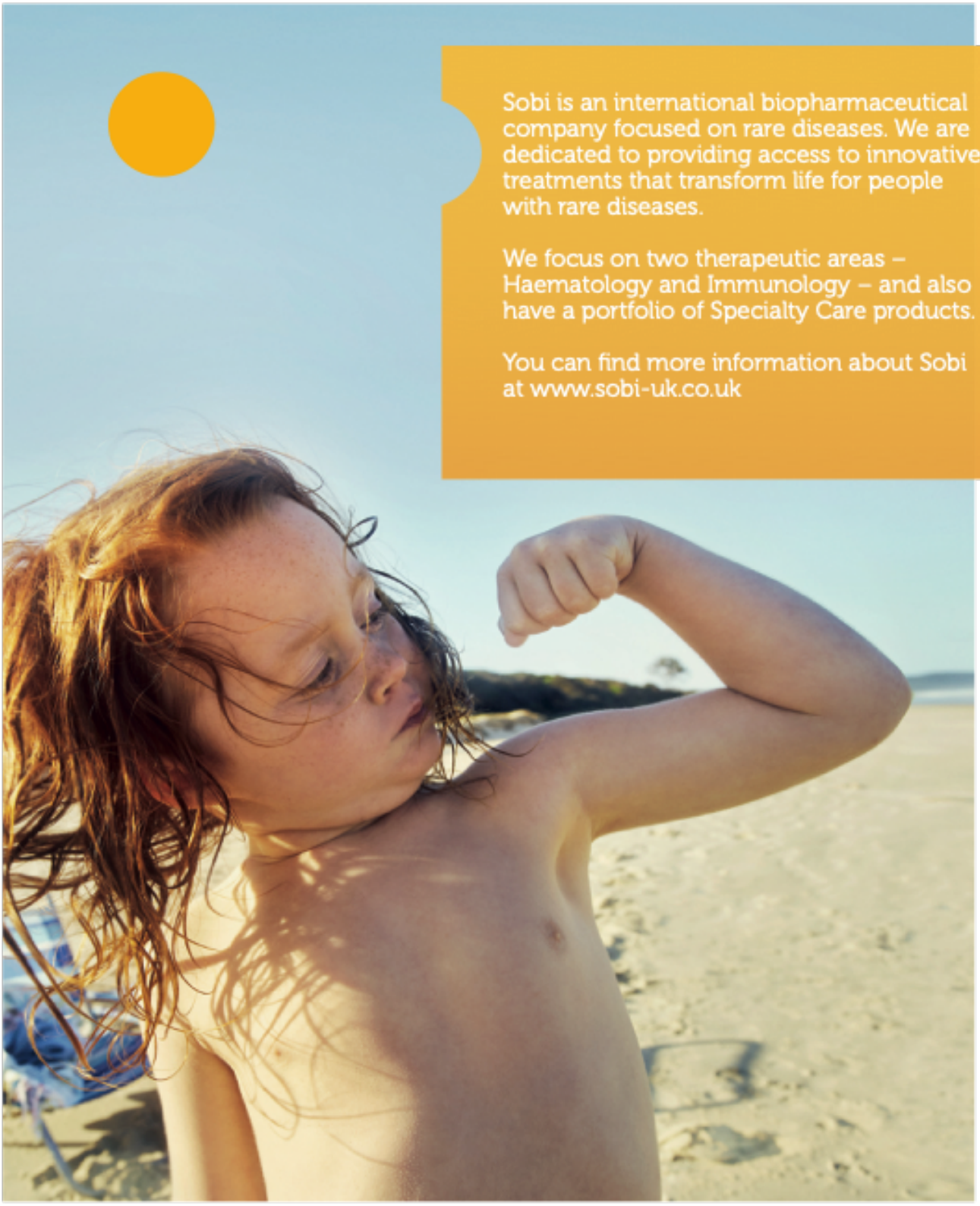

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Job Code: NP-16579 Date of preparation: May 2021

SPEAKER BIOGRAPHIES & ABSTRACTS

ADULT SESSION

THURSDAY 24TH JUNE

PERSONAL BACKGROUND

Radha Ramachandran
IMD Consultant
Guy's & St Thomas' Hospital, London

Following successful completion of core medical training, and membership of the Royal College of Physicians' UK examinations, Radha Ramachandran undertook her specialist training in Chemical Pathology and Metabolic Medicine at Imperial College Healthcare NHS Trust in London.

She completed her sub-speciality training in Adult Inherited Metabolic Diseases training at the National Hospital for Neurology and Neurosurgery, Queen Square and Evelina Centre of Inherited Metabolic Diseases and was appointed Consultant in Metabolic Medicine and Adult Inherited Metabolic Diseases (IMD) at the Centre for Inherited Metabolic Diseases at Guys and St Thomas' NHS Foundation Trust (GSTT) in Feb 2013. She was appointed Clinical Lead for the service in March 2017.

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REFERENCE: 1. Galafold Summary of Product Characteristics. Available at https://www.medicines.org.uk/emc/product/10934/smpc#gre

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Missed dose: Galafold should not be taken on 2 consecutive days. If a dose is missed, the patient should take the missed dose of Galafold only if it is within 12 hours of the normal time the dose is taken. If more than 12 hours has passed the patient should resume taking Galafold at the next planned dosing day and time according to the every other day dosing schedule. Elderly population: No dosage adjustment is required based on age. Renal impairment: Galafold is not recommended for use in patients with Fabry disease who have estimated GFR less than 30mL/min/1.73 m^2. Hepatic impairment: No dosage adjustment of Galafold is required in patients with hepatic impairment. Paediatric population: The safety and efficacy of Galafold in children aged less than 16 years have not yet been established. No data are available. Method of administration: For oral use. Galafold exposure is decreased by approximately 40% when taken with food and therefore food should not be consumed at least 2 hours before and 2 hours after taking Galafold to give a minimum 4 hours fast. Clear liquids, including carbonated drinks, can be consumed during this period. Galafold should be taken every other day at the same time of day to ensure optimal benefits to the patient. Capsules must be swallowed whole. The capsules must not be cut, crushed, or chewed. **Contraindications**: Hypersensitivity to the active substance or to any of the excipients. **Special warnings and precautions for use**: It is advised to periodically monitor renal function, echocardiographic parameters and biochemical markers (every 6 months) in patients initiated on or switched to migalastat. In case of meaningful clinical deterioration, further clinical evaluation or discontinuation of treatment with Galafold should be considered. Galafold is not indicated for use in patients with non-amenable mutations. No reduction in proteinuria was observed in patients treated with Galafold. Galafold is not recommended for use in patients with severe renal insufficiency, defined as estimated GFR less than 30mL/min/1.73 m^2. Galafold is not intended for concomitant use with enzyme replacement therapy. **Interactions**: See SPC. **Fertility, pregnancy and lactation**: Women of childbearing potential/contraception in males and females: Galafold is not recommended in women of childbearing potential not using contraception. Pregnancy: Galafold is not recommended during pregnancy. Breast-feeding: It is not known whether Galafold is secreted in human milk. A decision must be made whether to discontinue breast-feeding or to discontinue Galafold, taking into account the benefit of breast-feeding for the child relative to the benefit of therapy for the mother. Fertility: The effects of Galafold on fertility in humans have not been studied. **Effects on ability to drive and use machinery**: Galafold has no or negligible influence on the ability to drive and use machines. **Undesirable effects**: The most common adverse reaction was headache, which was experienced by approximately 10% of patients who received Galafold. Very common (≥1/10): headache. Common (≥1/100 to <1/10): depression, paraesthesia, dizziness, hypoaesthesia, vertigo, palpitations, dyspnoea, epistaxis, diarrhoea, nausea, abdominal pain, constipation, dry mouth, defaecation urgency, dyspepsia, rash, pruritus, muscle spasms, myalgia, torticollis, pain in extremity, proteinuria, fatigue, pain, blood creatine phosphokinase increased, weight increased. Uncommon (≥1/1,000 to <1/100), Rare (≥1/10,000 to <1/1,000), Very rare (<1/10,000), not known (cannot be estimated from the available data). **Overdose**: In case of overdose, general medical care is recommended. Headache and dizziness were the most common adverse reactions reported at doses of Galafold of up to 1250mg and 2000mg, respectively. **List of excipients**: Capsule contents: Pregelatinised starch (maize), magnesium stearate. Capsule shell: Gelatin, titanium dioxide (E171), indigo carmine (E132). Printing ink: Shellac, black iron oxide, potassium hydroxide. **Storage**: Galafold does not require any special temperature storage conditions. Store in the original package in order to protect from moisture. **Packs Size**: 14 capsules/pack. **Price**: £16153.85 per pack **Legal Category**: POM. **Marketing Authorization Holder**: Amicus Therapeutics Europe Limited, Block 1, Blanchardstown Corporate Park, Ballycoolin Road, Blanchardstown, Dublin, D15 AKK1, Ireland. **Marketing Authorization Number(s)**: EU/1/15/1082/001. **Date of Preparation of PI**: February 2021. Further information is available on request from Amicus Therapeutics, UK Ltd., Galafold is a registered trademark. © Amicus Therapeutics UK Ltd, Marlow, UK

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PP-GA-UK-0001-0521 May 2021

PERSONAL BACKGROUND

Dr Gisela Wilcox
BMedSc(Hons) MBBS(Hons MD FRACP MAACB FRCPA FRCP Edin

Dr Gisela Wilcox is Honorary Senior Lecturer (Teaching and Research), and Consultant in Metabolic Medicine at Salford Royal NHS Foundation Trust and University of Manchester in Manchester, United Kingdom having taken up this latter post in February 2013.

She is also Clinical Ambassador for Medics4RareDiseases a charity seeking to raise the awareness of rare diseases amongst medical students, junior doctors and ultimately the wider medical community.

Prior to this, she established in 2009, the first dedicated adult Inherited Metabolic Disorders service in Victoria, Australia, and been Consultant Physician in the Clinical Nutrition & Metabolism Unit at Monash Medical Centre, Victoria, Australia, since 2002. This centre included a stateof the art body composition laboratory with access to gold standard methodology established and developed by Professor Boyd J.G. Strauss.

Her background clinical training was in Adult Endocrinology (FRACP 1997) and in Chemical Pathology (FRCPA 1999), followed by a Fellowship in Metabolic Medicine at the Victorian Clinical Genetics Service & The Royal Children's Hospital in Melbourne during 1999-2001. Further experience in adult Inherited Metabolic Disorders was gained in 2009 at the Charles Dent Metabolic Unit at the National Hospital for Neurology and Neurosurgery in London, UK and the Adult Metabolic Disorders Clinic, Vancouver General Hospital, in Canada. She is also an experienced Chemical Pathologist/Clinical Biochemist, based at Melbourne Pathology (Sonic Healthcare) from 2004-2013.

Current and past academic positions include teaching and student supervisory roles from SSCP to MRes & PhD level, at the University of Manchester, Adjunct Senior Lecturer at Monash University, Department of Medicine (2003-2017) and Professorial Associate, School of Biomedical Sciences, Victoria University respectively (2005-2010).

Early clinical research work, from the late 1980s, was in phytoestrogens and their effects in postmenopausal women, leading to, and following from, her Bachelor of Medical Science degree. Having completed her Doctorate (Doctor of Medicine) by 14 published papers in 2015 on Phytochemicals in Human Health and Disease, ongoing research interests include this field, together with the potential interaction with probiotic organisms, body composition and nutritional status in adults with inherited metabolic disorders, neuropsychological impact of IMD, as well as other areas in clinical nutrition and metabolic medicine.

She has over 35 peer reviewed scientific papers, with total citations exceeding 4100, as well as over 65 abstracts and various lay publications.

Name of Presenting Author and Department:
Professor Rob Taylor

Wellcome Centre for Mitochondrial Research, Translational and Clinical Research Institute, Faculty of Medical Sciences, Newcastle University; NHS Highly Specialised Service for Rare Mitochondrial Disorders of Adults and Children, Newcastle upon Tyne Hospitals NHS Foundation Trust

Title of Abstract:

Developmental consequences of defective ATG7-mediated autophagy in humans

Co-Presenting Authors:

Jack J. Collier[1,2], Claire Guissart[3], Monika Oláhová[1,4], Souphatta Sasorith[3], Fumi Suomi[5], Florence Prion-Prunier[6], David Zhang[7], Nuria Martinez-Lopez[1,8], Nicolas Leboucq[9], Angela Bahr[10], Silvia Azzarello-Burri[10], Selina Reich[11,12], Ludger Schöls[11,12], Tuomo M. Polvikoski[2], François Rivier[13], Pierre Meyer[13], Lise Larrieu[3], Andrew M. Schaefer[1,2], Hessa S. Alsaif[14], Suad Alyamani[14], Stephan Zuchner[15,16], Inês A. Barbosa[17], Charu M. Deshpande[18], Angela Pyle[1,2], Fowzan S. Alkuraya[14], Mina Ryten[7], Agnès Delahodde[5], Anita Rauch[8], Matthis Synofzik[9,10], Robert McFarland[1,2], Thomas G. McWilliams[5,19], Michel Koenig[2] and Robert W. Taylor[1,2,20]

[1] Wellcome Centre for Mitochondrial Research, Newcastle University, Newcastle upon Tyne, United Kingdom
[2] Translational and Clinical Research Institute, Faculty of Medical Sciences, Newcastle University, Newcastle upon Tyne, United Kingdom
[3] EA7402 Institut Universitaire de Recherche Clinique, and Laboratoire de Génétique
Moléculaire, University of Montpellier and University Hospital, 34093 Montpellier, France
[4] Biosciences Institute, Faculty of Medical Sciences, Newcastle University, Newcastle upon Tyne, United Kingdom
[5] Translational Stem Cell Biology & Metabolism Program, Research Programs Unit, Faculty of Medicine, University of Helsinki, 00290, Finland
[6] Institut de Biologie Intégrative de la Cellule, Gif-sur-Yvette, France
[7] Reta Lila Weston Research Laboratories, Department of Molecular Neuroscience, University College London (UCL) Institute of Neurology, London, United Kingdom
[8] Faculty of Medicine, Albert Einstein College of Medicine, Bronx, NY, USA
[9] Neuroradiologie, CHU de Montpellier, Montpellier, France
[10] Institute of Medical Genetics, University of Zurich, Schlieren-Zurich CH-8952, Switzerland
[11] Hertie-Institute for Clinical Brain Research (HIH) and Center of Neurology, University of Tübingen, Germany
[12] German Center for Neurodegenerative Diseases (DZNE), University of Tübingen, Germany
[13] Department of Pediatric Neurology & Reference Center for Neuromuscular

Diseases AOC, CHU Montpellier, PhyMedExp, INSERM, CNRS, University of Montpellier, France
[14] King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia
[15] Dr. John T. Macdonald Foundation, Department of Human Genetics, FL33136 Miami, USA
[16] John P. Hussman Institute for Human Genomics, University of Miami, Miller School of Medicine, FL33136 Miami, USA
[17] Division of Genetics and Molecular Medicine, King's College London School of Medicine, Guy's Hospital, London, United Kingdom
[18] Clinical Genetics Unit, Guys and St. Thomas' NHS Foundation Trust, London, SE1 9RT, United Kingdom
[19] Department of Anatomy, Faculty of Medicine, University of Helsinki, 00290, Finland
[20] NHS Highly Specialised Service for Rare Mitochondrial Disorders of Adults and Children, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, United Kingdom

Abstract :

Autophagy is an essential developmental and homeostatic process, driving the endolysosomal degradation of protein aggregates, organelles and pathogens. Dysfunctional autophagy has been implicated in complex human diseases, yet congenital disorders of autophagy remain exceedingly rare. We identified pathogenic, bi-allelic ATG7 variants, encoding the principal driver of autophagy, in twelve patients from five families; all patients display a complex neurodevelopmental disorder distinguished by selective neurological, neuromuscular and endocrine dysfunction. Contrasting conditional Atg7 deletion in mice (causing perinatal lethality), patients survive into adulthood despite loss of ATG7. Patient fibroblasts displayed diminished autophagy, whilst the expression of mutated ATG7 failed to rescue autophagy-deficient model systems, supporting variant pathogenicity. ATG7-deficient patient muscle revealed myopathic changes, together with subsarcolemmal P62 accumulation. Despite loss of ATG7, autophagic structures were readily detected, suggesting that ATG7-independent autophagosome biogenesis pathways are sufficient to maintain basal, autophagic degradation in human cells. Our study provides the first clinical, genetic and mechanistic demonstration that mutated ATG7 leads to neurodevelopmental disease underpinned by defective, canonical autophagy. Importantly, two patients with undetectable ATG7 protein display a relatively mild phenotype, revealing that human life is compatible with the absence of a non-redundant, core autophagy gene, challenging current opinion regarding the role of autophagy in human health.

Name of Presenting Author and Department: Corey Pritchard
(Clinical Biochemistry, University Hospitals Bristol and Weston)
Title of Abstract: A case study of a patient with Aicardi-Goutières syndrome presenting as a possible Peroxisomal disorder
Co-Presenting Authors: Dr Vicki Warburton (Clinical Biochemistry, University Hospitals Bristol and Weston), Dr Helena Kemp (Clinical Biochemistry, North Bristol NHS Trust), Maryam Khan (Clinical Biochemistry, North Bristol NHS Trust), Dr Andrew A. Mallick (Paediatric Neurology, University Hospitals Bristol and Weston), Dr Andrew Lux (Paediatric Neurology, University Hospitals Bristol and Weston), Dr Emma Hulbert-Powell (General Paediatrics, University Hospitals Plymouth), Dr Efstathia Chronopoulou (Paediatric Metabolic Disease, University Hospitals Bristol and Weston).

Abstract :

We present a female who at 3 months old had abnormal movements and developmental delay. Plasma amino acids and plasma acylcarnitines showed no significant abnormalities. Urine organic acids (dilute sample) showed a trace of 2-hydroxysebacic and C14-epoxydicarboxylic acid. Very long chain fatty acid analysis (VLCFA) was advised. Repeat urine organic acids 1 month later were similar. MRI brain was normal (although suboptimal due to movement). At 7 months she had further investigations due to failure to thrive and faltering growth. She had a moderate patent ductus arteriosus (which was closed) and atrial septal defect. She was microcephalic and visually impaired. Repeat MRI brain showed cerebral volume loss, combined hypomyelination/dysmyelination, and high T2 and low T1 signal in the basal ganglia, adjacent frontal white matter and external capsules. Her EEG was abnormal and suggested subclinical seizures. Lysosomal enzyme analysis excluded MLD and Krabbe disease. Repeat urine organic acids showed significantly elevated 2-hydroxy sebacic and C14-epoxydicarboxylic acid. VLCFA profile showed increased C26:0, C26:0/C22:0 and C24:0/C22:0, suggestive of a peroxisomal disorder. Repeat VLCFA profile (pre-feed sample), bile acid intermediates and red cell plasmalogens was advised. However, rapid exome sequencing revealed a heterozygous de novo IFIH1 missense variant, NM_022168.4:c.2159G>A p.(Arg720Gln) associated with Aicardi-Goutières syndrome.

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PERSONAL BACKGROUND

Fanny Mochel
Associate Professor of Genetics
Sorbonne University Paris &
Consultant Neurologist, Reference Centre for Neurometabolic Diseases, Paris

Fanny Mochel is an associate professor of genetics at Sorbonne University. She received her MD in Genetics in 2005 at the University Paris Descartes, her PhD in Neuroscience in 2010 at Sorbonne University and is board certified in inborn errors of metabolism.

Dr Mochel leads the French reference center on Neurometabolic diseases in adults and runs a Neurometabolic research group at Paris Brain Institute of La Pitié-Salpêtrière University Hospital in Paris. She is chair of the adult section of the Society for the Study of Inborn Errors of Metabolism (SSIEM), council member of the SSIEM and co-chair of the French society for inborn of errors of metabolism in adults. Her research is focused on the characterization and treatment of brain energy deficiencies in neurometabolic and neurodegenerative diseases. Her major areas of expertise are the identification of neurometabolic biomarkers in vitro (metabolomics) and in vivo (metabolic imaging) as well as therapeutic approaches targeting the Krebs cycle.

Abstract

5,10-Methylenetetrahydrofolate reductase (MTHFR) deficiency usually presents as a severe neonatal disease. We wished to characterize natural history, biological and molecular data, and response to treatment of patients with late-onset MTHFR deficiency. We performed a retrospective collection from patients identified through the European Network and Registry for Homocystinuria and Methylation Defects and the Adult group of the French Society for Inherited Metabolic Diseases. To identify juvenile to adult-onset forms of the disease, we included patients with a diagnosis established after the age of 10 years.

We included 14 patients (median age at diagnosis: 32 years; range: 11-54). At onset (median age: 20 years; range 9-38), they presented with walking difficulties (n=8), cognitive decline (n=3) and/or seizures (n=3), sometimes associated with mild mental retardation (n=6). During the disease course, symptoms were almost exclusively neurological with cognitive dysfunction (93%), gait disorders (86%), epilepsy (71%), psychiatric symptoms (57%), polyneuropathy (43%), and visual deficit (43%). Mean diagnostic delay was 14 years. Vascular events were observed in 28% and obesity in 36% of the patients. One patient remains asymptomatic at the age of 55 years. Upon treatment, median total homocysteine decreased (from 183 µmol/L, range 69-266, to 90 µmol/L, range 20-142) and symptoms improved (n=9) or stabilized (n=4). Missense pathogenic variants in the C-terminal regulatory domain of the protein were over-represented compared to early-onset cases. Residual MTHFR enzymatic activity in skin fibroblasts (n=4) was rather high (17 to 58%).

In conclusion, this series of patients with late-onset MTHFR deficiency underlines the still unmet need of a prompt diagnosis of this treatable disease.

PRESENTATIONS FROM ABSTRACTS SUBMITTED

ABSTRACT

Name of presenting author: Charlotte Ellerton[1]

Title: Social, emotional and behavioural outcomes in children born to women with PKU and their relationship with maternal metabolic control.

Co-presenting authors: Lynne Aitkenhead[1], Rebecca Greenaway[2], Charlotte Ellerton[1], Robin Lachmann[1], Elaine Murphy[1]

Author affiliations:

1. Charles Dent Metabolic Unit, University College London Hospitals
2. Neurodisability Service, Great Ormond Street Hospital for Children

Without strict metabolic control, maternal phenylketonuria (mPKU) affects children's long-term development. Existing research has focussed on cognitive outcomes, especially IQ. We undertook a review of psychological outcomes on the Strengths and Difficulties Questionnaire and their relationship with maternal metabolic control in children attending a mPKU follow up clinic.

Data were available for 21 children aged 0-4 years and 57 aged 4-17 years. In 96% of pregnancies median phe concentrations met European guidelines. 69% started treatment before conception.

Children aged 0-4 years showed increased rates of hyperactivity (33% vs 8%, $p=0.003$) and peer problems (19% vs 8%, $p=0.035$) compared with published norms. Those aged 4-17 years showed increased rates of peer problems (19% vs 10%, $p=0.028$).

Hyperactivity ($r=0.28$ $p=0.015$) and prosocial behaviour ($r=-0.26$ $p=0.026$) correlated with median phe in pregnancy. Hierarchical regression was used to determine the extent to which the last recorded phe result before pregnancy treatment began and median phe during each trimester explained the variance in outcomes. Phe concentration before pregnancy treatment was commenced made a unique contribution ($p<0.038$).

Parents should be counselled on the importance of preconception treatment for optimal psychological outcomes, and children should be monitored for these difficulties.

Conflict of interest: This work was funded by a grant from the Nutricia Metabolic Research Foundation. Dr Lynne Aitkenhead has received honoraria and consulting fees from Nutricia.

ABSTRACT

Name of Presenting Author and Department: Faiza Adrees Mark Holland Unit, Salford Royal NHS Foundation Trust

Title of Abstract: The use of glycerol phenylbutyrate in adult patients with Urea Cycle Disorders- one centre experience.

Co-Presenting Authors: Dr. Reena Sharma, Dr. Gisela Wilcox, Dr. Ana Jovanovic and Dr. Karolina Stepien

Background:
Urea Cycle Disorders (UCDs) are a heterogeneous group of conditions caused by a defect in one of six enzymes. Variable clinical manifestations resulting from hyperammonaemia require lifelong low protein diet and ammonia scavengers (sodium benzoate, NaB, sodium phenylbutyrate, NaPB).

Methods:
Patients/ carers were contacted via telephone and questionnaire was used to assess their experience with current treatment with NaPB. Data on patient compliance, what they thought of taste and if they had experienced adverse reactions was collected. Where problems to existing therapy were identified, patients/carers were asked if they would like to consider switching to glycerol phenylbutyrate (GPB).

Results:
Amongst adults with UCDs, 65% remain on ammonia scavenger therapy, including 22% (10) patients taking NaPB either alone or in combination with NaB. 5/10 (50%) patients, with citrullinaemia and arginase deficiency, were switched due to various reasons including: dislike of taste, formulation and poor compliance to NaPB. Questionnaire was repeated 3 months after switching to GPB. Overall, compliance and acceptability improved significantly in patients who had switched therapy.

Conclusions:

Patients tolerate GPB. Overall, compliance improved for patients when switched to GPB. Apart from supply issues with syringes for administration, no other problems were identified. GPB is a good option for patients experiencing difficulties with NaPB.

ABSTRACT

Name of Presenting Author and Department: Katie Rawlins, Adult Inherited Metabolic Diseases Service, Guy's and St Thomas' NHS Foundation Trust

Title of Abstract:
Sitosterolaemia effectively managed with dietary modification + Ezetimibe

Co-Presenting Authors : Katie Rawlins[1, 2], Eun Ji Kim[3], Sarah Firman[1,2], Gemma Randles[1,2], Jennifer Cook[1, 2], Radha Ramachandran[2, 3], Anthony S Wierzbicki[3]
1 Department of Nutrition and Dietetics, Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom
2 Adult Inherited Metabolic Diseases Service, Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom
3 Chemical Pathology and Metabolic Medicine, Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom

Sitosterolaemia is an autosomal recessive condition caused by mutations in ABCG5 or ABCG8 genes. It results in defective excretion of xenosterols, causing tissue accumulation, and high circulating levels, of sterols. Patients present with tendon xanthomas and premature atherosclerosis. Preferred treatment option is Ezetimibe. Less is known about utility of dietary modifications.

A 29-year-old female presented with multiple large xanthomas secondary to sitosterolaemia [homozygote; ABC-G5 Arg446* mutation]. She was started on ezetimibe 10mg later incremented to 20mg due to limited initial response.
We reviewed the limited literature on sterol composition of foods, and advised her to (i) avoid nuts, seeds, chocolate, plant-based margarines, shortening, avocado, wheat germ, shellfish, seaweed and vegetable oils (olive oil was allowed in limited quantities) (ii) limit beans and pulses (iii) consume sources of lean protein e.g. chicken, turkey, lean red meat, eggs or reduced fat dairy (iv) eat potatoes, tubers and white carbohydrate sources (v) have fruits and vegetables freely.

Plasma sterol profile improved significantly over 7 months; Sitosterol 435 to 271μmol/L (38%), Campesterol 244 to 135 μmol/L (45%), Stigmasterol 17 to 13μmol/L (24%). There was also a perceptible decrease in size of xanthomas, demonstrating the effectiveness of combined ezetimibe and dietary intervention.

ABSTRACT

Name of Presenting Author and Department: Dr Bernd Schwahn, Willink Unit, Manchester

Title of Abstract: Results of general newborn screening for Isovaleric Acidaemia in the North-West of England

Co-Presenting Authors: Teresa Hoi Yee WU, Chern TAN

We audited adherence to laboratory and clinical management guidelines for general newborn screening (NBS) for isovaleric acidaemia (IVA) and the outcomes of screening positive babies in the North-West of England. Data were obtained from the NBS laboratories in Manchester, Leeds and Liverpool and we clinical data were retrieved from case notes of the Willink Unit.

From a cohort of over 1 million newborns screened over a period of almost 10 years, 27 were referred with a raised C5-carnitine. Adherence to laboratory standards was overall very good and clinical evaluation and confirmatory investigations were initiated in a timely fashion. Only 2/27 referrals were diagnosed with severe IVA and in 25/27 the diagnosis could not be confirmed. The vast majority had a false positive screening test due to maternal exposure to pivalic acid. One case was diagnosed with benign short/branched chain acyl-CoA dehydrogenase deficiency. One of the true positive cases had already been admitted to hospital when the NBS result was reported and the other was symptomatic at home when parents were recalled.

In conclusion, adherence to screening, diagnostic and clinical guidelines is satisfying. The screening process for IVA however has significant shortcomings and causes a high proportion of false positive notifications.

ABSTRACT

Name of Presenting Author and Department: Francesca Magrinelli, Department of Clinical and Movement Neurosciences, UCL Queen Square Institute of Neurology, University College London, London, UK

Title of Abstract:
Adult-onset generalised dystonia as the main phenotypic feature of alpha-methylacyl-CoA racemase deficiency.

Co-Presenting Authors:
Helen Grote, Carla Cordivari, Martin Koltzenburg, Mohsan Malik, James Acheson, Anna Latorre, Alice Gennari, Stephanie Efthymiou, Alkyoni Athanasiou-Fragkouli, Sacha Ferdinandusse, Charlotte Ellerton, Robin Lachmann, Peter T. Clayton, Henry Houlden, Kailash P. Bhatia, Elaine Murphy

Alpha-methylacyl-CoA racemase deficiency (AMACR-def) is a rare peroxisomal disorder affecting the metabolism of pristanate and bile acid intermediates. Biallelic mutations in the AMACR gene were first linked to adult-onset sensorimotor neuropathy with/without pigmentary retinopathy. A few reports have expanded the phenotypic spectrum from isolated transaminasemia to recurrent encephalopathic episodes.
We describe in detail three patients with AMACR-def presenting with adult-onset generalised dystonia as the main phenotypic feature. In addition, Patient 1 had migraine since adolescence and two encephalopathic episodes in her 20s, Patient 2 had a stroke-like episode with confusion and right homonymous hemianopia, whereas Patient 3 had no history of acute neurological events. Patients 1 and 2 also had retinopathy, but not peripheral neuropathy. All patients showed MRI-T2 hyperintensities in the midbrain, pons, and thalami, and increased serum pristanate concentration. Genetic testing revealed Patient 1 was compound heterozygote for two novel AMACR mutations, while Patients 2 and 3 (siblings born to consanguineous parents) were homozygotes for a different novel variant. Enzymatic assays on skin fibroblasts supported the diagnosis.
Recognition of the spectrum of presentation of AMACR-def phenotypes and careful follow up of patients prescribed a restrictive diet is crucial to establish whether lowering pristanate modifies the disease natural history.
Note: Patients have given permission to present their clinical information and video.

ABSTRACT

Name of Presenting Author and Department: Nazreen Banu Kamarus Jaman, GOSH, London

Title of Abstract:
SRD5A3-CDG: Emerging phenotypic features apart from the eye involvement.

Co-Presenting Authors: Dr Stephanie Grunewald (Consultant in Metabolic Medicine)

Background:

SRD5A3-CDG (CDG-Iq) is a rare N-glycosylation defect due to steroid 5 alpha reductase type 3 deficiency. Key feature is an early severe visual impairment with variable ocular anomalies often leading to diagnosis. Additional features are still ill defined. In this case study we discuss eleven genetically confirmed cases and report on emerging features involving other systems apart from the eye phenotype.

Methods:
Eleven SRD5A3-CDG patients of five sets of sib ships were included in the study. Data on nine of eleven patients are yet unpublished. Patients' results on biochemical and genetic investigations and on in depth phenotyping are presented.

Results:
Key diagnostic features of SRD5A3-CDG are ophthalmological abnormalities such as retinitis pigmentosa, retinal dystrophy and optic nerve hypoplasia. SRD5A3-CDG is also characterized by variable neurological symptoms including intellectual disability, cerebellar abnormalities, movement disorder hypotonia, ataxia, autism and anxiety disorder. Also ichthyosiform skin lesions, joint laxity and scoliosis have been observed in our cohort.

Interestingly four out of five sib ships were duos, and one family presented with three affected siblings.

SPEAKER BIOGRAPHIES & ABSTRACTS

Scientific

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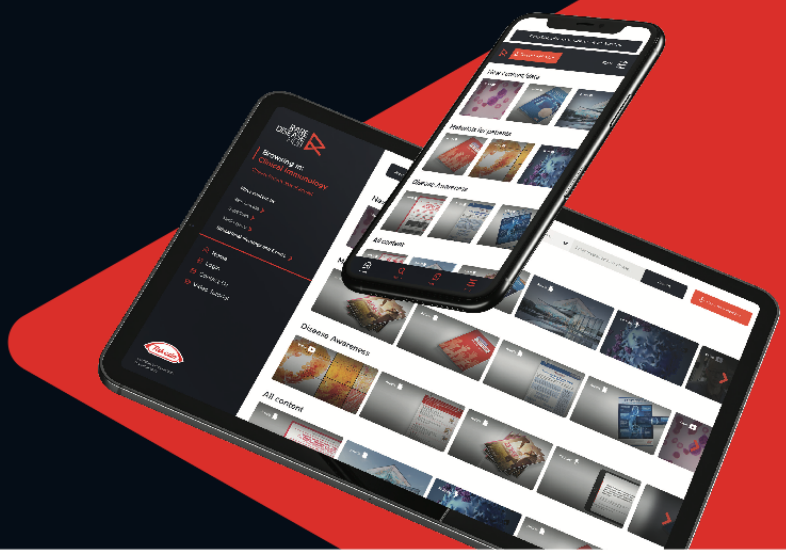

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PERSONAL BACKGROUND

Heather Church
Willink Biochemical Genetics Unit,
Manchester University NHS Foundation Trust

Heather graduated with a BSc in Biology and Chemistry from Goldsmith's College, University of London in 1987, followed by a Ph.D. from the Department of Chemistry, University of Manchester in 1991. She then worked as a research scientist within the Department of Obstetrics and Gynaecology, University of Manchester from 1991-1999 studying cell adhesion and the role of extracellular matrix in human implantation.

In 1999 Heather took up the position of Clinical Biochemist in the Willink Biochemical Genetics Unit, now part of the Genomic Diagnostic Laboratory, and is currently jointly responsible for the management of the Lysosomal diagnostic service. Specific areas of interest include the longitudinal monitoring of treatment efficacy for LSD patients, and development of new laboratory services to enhance evaluation of patient outcomes.

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PERSONAL BACKGROUND

Teresa Hoi-Yee Wu

Consultant Clinical Scientist and Director of the Willink Biochemical Genetics Laboratory
Willink Biochemical Genetics Laboratory, Central Manchester University NHS Foundation Trust, Manchester, UK

Teresa was studying remyelination mouse models of multiple sclerosis at Imperial College London before Clinical Scientist training at Guy's & St Thomas' in 2001. She received specialist training in inborn errors of metabolism at Great Ormond Street Hospital.

In 2008 Teresa moved to the Willink Laboratory in Manchester as Principal Clinical Scientist in the Newborn Screening and Metabolites services. She is now Director of the Wilink Biochemical Genetics Laboratory.

Teresa has implemented a number of tests using tandem mass spectrometry to improve the laboratory diagnostic services, including plasma oxysterol for early diagnosis of Niemann Pick disease type C.

She is currently working on blood spot screening and early diagnosis of lysosomal storage diseases that are treatable, so that patients could receive treatment at the right time for maximal benefits.

PERSONAL BACKGROUND

Katherine Booth
Clinical Scientist
Willink Unit, Manchester

Katherine raduated with a degree in Biochemistry from the University of Manchester and then went on to study for a master's degree in biomedical and Forensic studies, graduating in 2003.

She started working for Manchester Foundation Trust in the Pancreatic Laboratory in 2004 and then went on to join the Willink Biochemical Genetics Laboratory in 2007 working in the field of Lysosomal Storage disorders where she is a senior Biomedical Scientist within the section.

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MAT-GAL-UK-000120 Date of Preparation: May 2021

PERSONAL BACKGROUND

Simon Jones, Manchester (United Kingdom)

Simon Jones is a consultant in paediatric inherited metabolic diseases at the Willink Unit at St. Mary's Hospital in Manchester, UK.

His major research interest is therapy for lysosomal storage diseases (LSDs).

He received his medical training at the Edinburgh University Medical School, Edinburgh, UK, with a BSc in Neurosciences. He moved to London and trained in Paediatrics at Guy's and St. Thomas' Hospital, London, UK. He has been working at the Willink Biochemical Genetics Unit in Manchester, UK since September 2005. Since 2008, he has been a consultant in paediatric inherited metabolic diseases at the Willink Unit and is now the clinical lead for the LSD service. The Willink Unit is now part of the Manchester Centre for Genomic Medicine at St. Mary's Hospital, Manchester, UK. He is the medical director of the NIHR Manchester children's clinical research facility.

Dr. Jones has been actively involved in many phase I-IV international multicentre trials of novel therapies for LSDs. He is currently the principal investigator in a number of LSD trials, and a senior lecturer at the University of Manchester. He is an author of over 60 peer-reviewed papers and 3 book chapters.

When not working, he watches Liverpool Football club and spends time with his family.

Abstract

Development of clinically relevant antibody monitoring in Enzyme Replacement Therapy

S A Jones, K L Brammeier, A Broomfield, A Ghosh, K L Tylee, H J Church
Enzyme replacement therapy has an important role in the treatment of patients with lysosomal storage disorders but the emergence of an anti-drug antibody (ADA) response can limit its efficacy and lead to a reduced biochemical and clinical outcome. Few laboratories are capable of detecting and quantifying this immune response and turn-around times for these assays can be poor. Detection of an ADA immune response allows early clinical intervention, but results need to be available in a timely manner to inform clinical care. Driven by this clinical need the Willink Biochemical Genetics Unit have validated to comply with ISO 15189:2012 standards an immunoglobulin G enzyme linked immunosorbent assay (ELISA) and cellular uptake inhibition assay to determine immune response to infused protein for Mucopolysaccharidosis Type I , Lysosomal acid lipase deficiency and work is ongoing for Mucopolysaccharidosis Type II.

A two-tier testing strategy has been employed. A primary screen by ELISA allows detection and quantification of IgG antibodies in a titre-based approach; this does not assess functional nature of the response. The second-tier test is a functional assay to identify whether detected antibodies exhibit neutralising activity towards the enzyme by measuring the uptake inhibition of enzyme by diseased cells. Assessment of cell lysate after the uptake of enzyme by cells allows interpretation of the catalytic activity and cellular uptake in a single quantifiable assay.
These data can be correlated with biomarker and clinical response to ERT to facilitate intervention strategies. Management of patients who have developed a persistent inhibitory immune response will be discussed.

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PERSONAL BACKGROUND

Helena Kemp
Consultant Chemical Pathologist
North Bristol NHS Trust

Dr Helena Kemp is a Consultant Chemical Pathologist at North Bristol NHS Trust, where she runs an Adult IMD clinic, the SW Regional Biochemical Genetics Laboratory. She is also Laboratory Director of the South West Regional Newborn Blood Spot screening programme.

Helena is currently Chair of the National Metabolic Biochemistry Laboratory Network (MetBioNet) and sits on the Metabolic Clinical Reference Group (CRG) and the NHS IMD Screening Advisory Board (IMDSAB).

Abstract

Inherited Metabolic Disorders (IMD) monitoring on patient collected samples (& COVID-19)

A number of improvements and innovations to clinical pathways have arisen as a consequence of the COVID-19 pandemic. Once such innovation is the provision of remote/virtual clinics and it is likely that this form of consultation will continue as part of routine service delivery. A limiting factor for the provision of such clinics, especially for IMD services, is the availability and access to specialist blood tests local to the patient and easy access to the results. Increasing the use and availability of testing patient collected samples for monitoring IMDs addresses some of these issues and offers many other practical, clinical and potentially financial benefits to support patient care.

Monitoring of patients with inherited metabolic disorders using dried blood spot specimens has been in use since the introduction of newborn screening for phenylketonuria (PKU) in the 1960's. Advancements in analytical technology have led to the development of numerous assays to enable monitoring of patients with a variety of different IMDs on finger prick samples collected by the patients themselves and mailed to the laboratory. There are however many factors including pre-analytical, analytical and post-analytical variables that can affect the final results and potentially influence their clinical utility. It is important that these factors are well understood and are controlled where possible to optimise the quality and accuracy of results and their appropriate application to clinical management and treatment guidelines.

A MetBioNet workshop was organised in August 2020 to explore the current provision of laboratory testing of patient-collected samples, the factors that affect the quality of results and the work required to standardise and optimise current practice to enable increased testing for the future. The key findings of the workshop will be presented along with the proposals to address the broader initiatives, through a joint MetBioNet and BIMDG working group, which will be required to develop and deliver high quality IMD monitoring on patient collected samples.

BIMDG

British Inherited Metabolic Diseases Group