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LIFE-TRANSFORMING NUTRITION
METABOLICS

Summary of presentations

Global Nutricia Metabolics Expert Day

7th June 2023
Nutricia Research Centre
in Utrecht, the Netherlands

SUMMARY OF PRESENTATIONS

As part of our ongoing commitment to provide high quality scientific education to support healthcare professionals continuing development, we also appreciate the value an in person meeting can bring with networking opportunities, best practice sharing and gaining insights for building research collaborations. As a result, we held our first ever live face to face Global Nutricia Metabolics Expert Day on 7th June 2023 in our Nutricia Research Centre, Utrecht, The Netherlands.

Herein follows a summary of the presentations given on the day.

We are currently undergoing a complete evaluation of the impact of the day with a view to repeating the event in 2024. Please contact your local Nutricia Metabolics representative for further details.

Dr. Carmen Rohde RD

University of Leipzig Medical Center, DE

Dr. Carmen Rohde is a dietitian working in the paediatrics department of the university clinics of Leipzig, Germany. Since 2004 she is treating a wide range of paediatric conditions. Her treatment focus are metabolic diseases, which she could enlarge into the adult department as well. In parallel, she works as a research dietitian and finished her PhD in the field of dietary PKU treatment. Her further research and publications were and are devoted to optimize PKU treatment, especially from a dietetic point of view.
She represents Germany for the SSIEM dietitians' group.

1. The changing face of PKU - the challenges of nutrition and dietetics in the area of new treatment approaches

Dr. Carmen Rohde gave an overview of the different stages in the management of PKU patients since the 1960s, highlighting the main challenges at each period.

Firstly, around the 1960s, "basic treatments" appeared and developed, changing the face of the disease by preventing neurological symptoms. This was the beginning of specialised dietary approaches, with the development of different types of protein substitutes. These were made from casein or bovine serum and contained a small amount of phenylalanine. In addition, there were no complete formulas or complete 'protein substitutes' or 'medical foods'. Low-protein foods had to be home made and preparation was long and complicated. The main challenges of this period were learning how to prepare an edible food formula and tasty recipes.

Then, in the 1970s, the "classic treatment" appeared, with mixtures of amino acids containing all the essential micronutrients and no phenylalanine, and special low-protein foods. Complex calculations were needed to obtain an accurate assessment of the amount of phenylalanine in the diet. The main challenges were to teach families how to calculate Phe accurately, and to help patients and parents to adhere to the strict diet. The question of how strict the diet should be was also a challenge. Around 2000, the "adapted diet" was developed, allowing families and patients to "relax" the strict diet. Vegetables and fruit with a phe content of less than 75mg/100g could no longer be weighed, as hypoprotein foods (<10mg Phe/100g). The main challenges were to ensure that patients could distinguish free foods from foods to be estimated. Other issues were how to eliminate the taste of the protein substitute and how to enable patients to participate in a normal social life.

Then, around 2007, cofactor therapies were introduced, making it possible to treat BH4-responsive patients with BH4. Neonatal/non neonatal BH4 loading tests and criteria of responsiveness were described. Treatment with BH4 made it possible to increase patients' tolerance of natural proteins, leading to lower or no intakes of protein substitutes. The challenges were to learn how to perform the BH4 loading test, and more particularly to manage the diet during the BH4 loading test for older patients. Another new challenge was to ensure that patients received sufficient protein and micronutrients. Practical case reports were presented and the monitoring procedures of patients treated with BH4 were demonstrated.

Finally, since 2021, enzyme therapy pegvaliase, for patients over 16 years of age, is available, increasing the possibilities of treatment. The aim of the enzyme therapy is to achieve reliable control of Phe blood levels throughout life, thereby improving cognitive and psychological symptoms while gradually consuming diets without protein restriction. With pegvaliase patients can gradually improve their protein intake. Various publications have been published setting out the recommendations of PKU experts, who have drawn up guidelines for the diet under pegvaliasis. The new challenges in this area are therefore to manage the diet at the start of therapy and to support patients throughout the various stages of introducing this new therapy. It is important to ensure an adequate intake of micronutrients (taking into account the ingested intake and plasma concentrations) and to deal with the anxiety and other psychological aspects associated with the liberalization of the diet.

The question of the next challenges to be faced with emerging therapies was raised…

Main references:

Adams et al. *Molecular Genetics and Metabolism* 2021
Longo et al. *Genet Med* 2019
Muntau et al. *Orphanet J Rare* Dis 2018
Rocha et al. *Mol Genet Metab Rep* 2021
Viau et al. *Molecular Genetics and Metabolism* 2021

Annemiek van Wegberg RD

Radboud University Medical Centre, Nijmegen, NL

Annemiek van Wegberg received her BSc degree in dietetics in 2009 and her MSc degree in clinical epidemiology in 2011. She has worked as a dietitian since 2009 in Radboud University Medical Centre Nijmegen, the Netherlands and specialized in peadiatrics and metabolic diseases from January 2010 onwards. Starting in February 2013, she worked for 3.5 years as the project assistant in the development of the first European PKU guidelines (which we are currently updating). In 2016 she started a PHD in Phenylketonuria at University Medical Centre Groningen, the Netherlands.

2. Update on European Guidelines

Annemiek van Wegberg explained the context of great disparities in the management of patients between European countries which led to the first guidelines being drawn up in 2013. Over time, it has become clear that further updates are needed and since 2018 a working group has been considering new recommendations. These new recommendations will be published in the next few months (by the end of 2023).

The method used to produce the guidelines was described, in particular the need to change methods (GRADE vs SIGN). Precision about the composition of the working groups and the organization of the meetings were added. Between June 2019 and now, three face to face meetings, one hybrib and nine virtual meetings were organized to elaborate the new recommendations.

The latest new developments in the guidelines were presented:

- Addition of DNAJC12 deficiencies in differential diagnosis of newborn screened with hyperphenylalaninemia: DNAJC12 deficiencies can be detected in case of normal pterins and dihydropteridine reductase activity when PAH genotype does not reveal 2 explaining variants.
- Addition of glycomacropeptide (GMP) in dietary management options: GMP is safe and suitable to use as a protein substitute in patients with PKU aged ≥4 years providing its phenylalanine content is considered in daily phenylalanine allocation.
- Neurocognitive test battery to use.
- Addition of pegvaliase in treatment options: Patients with PKU >16 years of age who are not able to achieve metabolic control with either diet or pharmacological treatment with sapropterin dihydrochloride should be offered treatment with pegvaliase.

Main discussions regarding the setting of target phenylalanine levels were exposed. The notion of inter-individual variability in tolerance was addressed, as was the potential mental and neuropsychological impact of the need to adhere to a very strict daily diet. One of the challenge is for stating about adults recommendations. As a matter of fact, there is something happening in the brain on neuro-radiology (MRI / MRS / PET studies) and outcome of some patients is not optimal. However, it is not currently possible to distinguish the effect of Phe levels in adulthood from that of Phe levels during different periods of life. In addition, the long-term effect of Phe level in adulthood is unknown. Finally, we are currently unable to clearly distinguish the effect of burden of treatment and Phe. Phenylalanine target in the new guidelines would be for PKU children: 120-360µmol/l and for adolescents: 120-600 µmol/l. For PKU adults it seems not clear yet how to describe and for maternal PKU: 120-360 µmol/l.

Main references:

Hagedom et al. *Orphanet Journal of Rare Disease* 2013
Mac Donald et al, *Orphanet Journal of Rare Disease* 2020
Van Spronsen et al. *Lancet Diabetes & Endocrinology* 2017
Van Wegberg et al. *Orphanet Journal of Rare Disease* 2017

Dr. Erin MacLeod RD

Director of Metabolic Nutrition, Rare Disease Institute, Children's National Hospital, Washington DC, USA

Erin MacLeod is Assistant Professor of Paediatrics at the George Washington University School of Medicine and Health Sciences as well as the Director of Metabolic Nutrition at Children's National in the Rare Disease Institute in Washington DC. She received her PhD from the University of Wisconsin where her research focused on GMP for the nutritional management of PKU. She has spent the past 13 years treating a variety of patients with inborn errors and along with PKU, has developed a particular passion for the treatment of urea cycle disorders. She has been an active member of GMDI serving on the Research, Communications, and Conference Planning Committees. She is now current President of GMDI as well as an active board member of SIMD.

3. Safety and efficacy of GMP

Dr. Erin MacLeod first exposed the discovery of the composition of GMP by scientists in Wisconsin, a cheese-producing region. As this type of protein is naturally low in some amino acids, including phenylalanine, the idea of using GMP-based products for certain metabolic diseases was born. Other properties attributed to GMP have also been described.

GMP-based protein supplements were offered to patients, and it appeared that the taste was better than those of amino-acids mixtures. Thus, compliance with the diet seemed less difficult. However as GMP contains a small amount of phenylalanine it was therefore imperative to ensure that the metabolic equlibrium of patients taking GMP was nevertheless correct. This seems to be the case in short- and medium-term studies, especially as the majority of patients do not use 100% GMP as a protein supplement. For some patients the amount of natural protein should be decreased in a little proportion to avoid an increase of phe levels with the introduction of GMP.

Moreover, it appears that the acid load provided by amino acid mixtures has an impact on the quality of bone mineralisation, with BMD correlating negatively with the amount of AA mixture taken. So, in addition to better compliance with dietary treatment, it seems that patients on GMP also have better bone status over time.
After, the speaker made a brief summary of the care of a child screened for hyperphenylalaninaemia in the USA, which is a little different from that practised in Europe. In USA, newborns screened with phenylalanine levels above 360 umol/l are put on a low-protein diet; at 5-6 months of age, BH4 sensitivity is tested regardless of genotype. For patients requiring a hypoprotein diet, GMP is usually introduced at 12-15 months of age, combined with a "simplified diet" (medical foods containing less than 20 mg Phe/100 g and natural foods <75 mg Phe/100g are not restricted). As the GMP amino acid blend contains a small amount of phenylalanine, it may be necessary to reduce the amount of food containing natural proteins (such as milk) when introducing GMP to infants, in order to keep blood phenylalanine levels within the tolerated range. Finally, it seems that all patients can benefit from GMP-based blends. Nevertheless, the best indications seem to be: patients who partially respond to BH4 (due to a better tolerance of natural proteins), children at the time of transition between infant and toddler blends, and for adults who are returning to a more restricted diet after having released it.

The main advantages of GMP-based protein substitutes, in addition to improved palatability, would be the fact that the proteins are intact and not hydrolyzed, and the beneficial effects of this on patients' bone status.

Strategies for use need to be defined on a case-by-case basis, with some patients preferring standard AA mixtures. It is also possible to combine several types of protein substitute (mixtures of amino acids and GMP).

Finally, because of its properties, future potential uses for GMP are discussed, such as its use in protein substitutes for patients suffering from tyrosinemia or arginase deficiency, or in the composition of low-protein products.

Prof. Elvira Verduci

Associate Professor in Pediatrics at University of Milan & Head of Metabolic Disease Unit, Vittore Buzzi Children's Hospital, Milan, IT

Elvira Verduci graduated Medical Doctor at the School of Medicine of the University of Milan Italy in 1998. Degree at the Post-Graduate School of Pediatrics of the University of Milan Italy in 2003. Clinical nutrition doctor's degree's at University of Milan in 2006. From 2013 to 2016 Researcher in Pediatrics letter A and from 2017 to 30 March 2020 letter B) at University of Milan, Department of Health Sciences, San Paolo Hospital. From 31 March 2020 Associate Professor in Pediatrics at University of Milan. From February 2023 Head of Metabolic Disease Division at Department of Pediatrics, Ospedale dei Bambini Vittore Buzzi Milan Italy, University of Milan, Italy. She is the referral recipient for the Rare Diseases Registry at Buzzi Children's Hospital for Congenital defects in aminoacid metabolism and transport RCG040.

From 2002 She has been involved in different European Community Projects (main topics metabolic programming, childhood obesity).

2017 – 2020 Member of Committee of Nutrition- European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN). From 2021 Secretary of Committee of Nutrition- European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN).

Main expertise in nutrition and metabolism, both in clinic and research aspect. Particularly involved in infant and child nutrition for the prevention of later non-communicable disease, in the management of vegetarian/vegan diet in children, in nutritional management of difficult circumstances (malnourished children, children affected by eating disorders or inborn errors of metabolism).

The number and type of publications, the invited talks and the oral presentations in meeting, the international collaborations can support this expertise (H index 38; 233 papers; 5131 citations) .

4. Effect of GMP on gut microbiota of patients with PKU

Pr Verduci began by outlining the composition of the intestinal microbiota and its role in various metabolisms (short-chain fatty acids, neurotransmitters, etc.). The importance of diversity in the microbiota in terms of the richness of the different species, but also in terms of the quantities of each species, was emphasised and illustrated by examples of pathological conditions in which alteration of intestinal microbial diversity has been observed (inflammatory diseases, allergies, neurodevelopmental disorders, metabolic syndrome, etc…). The concept of communication between the various organs, and the involvement of the microbiota is also explained (with the notion of microbiota-gut-brain axis, or microbiota-gut-liver axis).

Based on the observation that overall dietary glycemic index and glycemic load are higher in PKU than healthy children, the composition of the intestinal microbiota was studied in these patients. Studies show that phenylketonuria classical diet promotes shifts in firmicutes population, and that phenylketonuric diet negatively impacts on butyrate production. GMP is a protein substitute that differs from the amino acid mixtures traditionally used in the management of PKU patients and which has recently come into use. GMP is composed of macropeptides (and not just amino acids) which is associated with improved palatability.

Pr Verduci presented a study aimed to evaluate the possible effect of a GMP diet on the microbiome in PKU patients by investigating the gut microbiota and SCFAs concentration in stool samples before and after GMP supplementation in dietary treatment for a short period (the PIGPEN Study). Alpha-diversity did not show significant differences after the GMP supplementation period, and, similarly, GMP patients did not show a net dissimilarity over time in the betadiversity. However, bacterial groups analysis revealed a (non-significant) reduction in the Verrucomicrobia phylum and a trend toward an increase in the Firmicutes during the GMP intake. More specifically, the relative abundance of Agathobacter was increased following dietary modifications, with a possible implication in the optimization of vitamin D metabolism and phenylalanine metabolism. The impact of GMP on the bioavailability of tyrosine and tryptophan is also being studied, with a possible improvement in bioavailability when these amino acids are supplied by GMP, compared with AA mixtures. Thus, studies on PKU are giving importance to possible impact of alterations of gut microbiota on the central nervous system, also investigating the involvement of metabolic pathways.

The possible link between gut microbiota and the brain in IEMs, focusing on tryptophan metabolism in PKU is also discussed. Other pre-clinical studies also suggest that GMP is able to preserve cellular vitality, and to rescued the oxidative and anti-inflammatory balance, and could be a safer product than mixture of amino acids. Long term clinical studies are expected to evaluate if the GMP can contribute to the improvement of the health status of patients on long-term PKU diet. Finally, the effect of GMP in other conditions (obesity) is also presented with prospects for new studies….

Main references:

Bassanini et al. *Front Cell Infect Microbiol* 2019
Mayer et al. *Gastroenterology* 2014
Montanari et al *Nutrients* 2022
Canfora et al. *Nat Rev Endocrinol* 2019
Verduci et al. *Nutr Metab Cardiovasc Dis* 2018
Verduci et al. *Front Physiol* 2021

Dr. Nikolas Boy

Metabolic Paediatrician, Heidelberg University Hospital, DE

Dr. Nikolas Boy is working as metabolic pediatrician and child neurologist at the Children's Hospital in Heidelberg since 2009. After his specialization in Pediatrics in 2014, he focussed on clinical work and scientific projects in the field of metabolic medicine.
Starting with his dissertation in 2008, glutaric aciduria type 1 (GA1) became his main research focus.

Since 2015 he is the coordinator of the GA1 guideline group and since then has finalized two guideline revisions. In 2019, he received his Venia Legendi/Habilitation for the postdoctoral thesis *'Clinical long-term outcome and success of therapy in glutaric aciduria type 1'*. His main research activities comprise long-term outcome and disease variants in GA1 and other organic acidurias as well as urea cycle defects. Furthermore, he is the study site coordinator for the patient registry and natural history study within the German network for mitochondrial disorders (mitoNET).

5. How guideline development helps in optimising outcomes in glutaric aciduria type 1

Dr. Nikolas Boy began by recalling the enormous benefit of newborn screening (NBS) for glutaric aciduria type 1 (GA1). The prognosis of patients is transformed, with polyhandicap avoided in the vast majority of affected individuals.

Next, the metabolic pathways involved in GA1 are outlined, with 2 categories of patients with regard to urinary excretion of glutaric acid: high excretors (HE) and low excretors (LE). Studies of the natural history of GA1 have shown that there is the same risk of acute striatal attack (resulting in neurological disability) in HE and LE patients.
The history of the various guidelines is then reviewed, along with the main differences (in terms of methodology, key questions asked, studies available, levels of recommendations) between the 3 previous versions (first version 2007, first revision 2011, second revision 2017) and the latest revision (2022). So, updates are and will be required on a regular basis.

The data from the new guidelines are then presented.
Diagnosis of GA1 is made after NBS, but also after target work up in case of clinical suspicion (for example in case of no newborn screening or false negative of NBS, or characteristic neurological or neuroradiological abnormalities).
Data collection from screened patients showed that despite NBS and treatment, 1/6 of GA1 patients developed subdural hematoma (SDH), spontaneously or after minor trauma, within the first 3 years. SDH was found exclusively in HE patients and was always associated with extrastriatal anomalies, but not with macrocephaly. This observation has led to the modification of certain recommendations in the guidelines (recommendation 20): "Patients should be admitted to a hospital and closely monitored for at least 24h after a minimal or mild head trauma within the first 3 years of life due to the increased risk for developing SDH".

With regard to treatment, the concept of "combined metabolic treatment" is outlined. Maintenance treatment should be supervised by an experienced specialist centre. A low lysine diet is recommended up to the age of 6 years (level of recommendation A, strong recommendation) and carnitine should be supplemented lifelong aiming to maintain the concentration of free carnitine in plasma or blood spot within the reference range (level of recommendation B). After 6 years of age (level of recommendation B), the diet is liberalized but continued, and turned to a controlled protein intake using natural protein with low lysine content and avoiding lysine-rich food. For setting up the diet, the GA1 Parental Guide can be used as a practical implementation aid.

Metabolic emergency treatment is strongly recommended before 6 years, within the vulnerable period for striatal injury (level of recommendation A, strong recommendation). After 6 years, the level of evidence is low: « the metabolic emergency treatment can be administered during episodes of severe illness or perioperative management ». So the metabolic emergency treatment is recommended after 6 years, even if there are discussions and uncertainties.

Dr. Boy then presented a prospective follow-up study of GA1 patients diagnosed by NBS in Germany (since 1999), which is one of the two largest published cohorts of GA1 patients identified by NBS in the world. This study shows that treatment quality has the strongest impact on neurological outcome, in terms of prevention of striatal damage. He also points out that, as stated in the guidelines, a diet low in lysine is associated with a better prognosis than a low protein diet without calcuation of lysine.

In conclusion, clinical research influences guidelines development improving strengths of treatment recommendations. Concomitant prospective long-term outcome studies in parallel to the revision of guidelines has helped to unravel the relative impact of single therapeutic interventions on outcome, to improve level of evidence and to continuously upgrade recommendations for NBS and treatment, and to identify the level of risk of striatal damage in case of non-adherence to recommendations.

Some questions are still open, like the impact of biochemical phenotype on extra-striatal injury patterns and on cognition, or the impact of treatment quality on kidney function.
Studies will be needed to clarify long-term outcome and phenotypic spectrum of patient treated after NBS, or to assess the necessity and intensity of dietary lysine restriction or the indications for emergency treatment in adolescent and adult patients. Moreover, the optimal amount and effects of L-arginine intake aiming at additionally reducing intracerebral GA concentrations has to be defined. Finally, clinical relevance of progredient extrastriatal manifestations or kidney abnormalities (independent from treatment) and their need for clinical monitoring are addressed.

Main references:

Boy et al. *Ann Neurol*, 2018
Boy et al. *J Inherited Dis* 2018
Boy et al. *J Inherited Dis* 2022
Harting et al. *Brain* 2009
GA1 Parental Guide, 1st revision 2018
Märtner et al. *Sci Rep*, 2021
Strauss et al. *Mol Genet Metab*, 202

Dr. Anita MacDonald RD

Consultant Dietitian, Birmingham Women's and Children's Hospital, UK

Dr. Anita MacDonald OBE is Consultant Dietitian in Inherited Metabolic Disorders at Birmingham Children's Hospital, and an Honorary Professor in Dietetics at Plymouth University, UK. Although she semi-retired 7 years ago, she is even more involved in PKU work, concentrating solely on this group as well as doing some voluntary work for the National Society for PKU (NSPKU).

Her involvement in inherited metabolic disorders (IMD) has spanned almost all her working life (>40 years).

Dr. MacDonald obtained her PhD in phenylketonuria (PKU) in 1999. She has directly cared for over 400 patients with PKU. She has always been involved in PKU research, supervises PhD students, Master students and lectures worldwide on PKU. She has around 450 publications – many are research publications on PKU.

She is a member of the European PKU Guidelines group (which is aiming to standardise PKU care across Europe), is a member of ESPKU Scientific Advisory Committee, and member of the UK NSPKU Medical Advisory Panel.

The retirement slippers remain well and truly in their box!

6. UK dietary practices for tyrosinemias type I, II, III: time for change

Taking into account the heterogeneity in dietary management between health care teams (national and international), the lack of guidelines and the differences in management between patients with different types of tyrosinemia (HT), Dr. Anita MacDonald presented the work aimed at harmonising the diets prescribed to tyrosinemia patients in UK centres.

The main principles of dietary management of patients should be as follows: the diet must be consistent, logical, effective, straightforward and easy to implement for families and health professionals. Moreover, no dietary management should be unnecessarily restrictive.
All the UK centres specializing in the management of metabolic diseases and receiving patients with HT (children and adults) took part in this work, which was organized in 5 virtual meetings over a 12-month period. The work consisted in describing the dietetic practices in the centres and assessing the current state of knowledge. This served as a starting point for developing a consensus on the management of patients with tyrosinemia

The data collected made it possible to describe the cohort of patients followed in UK: 65 patients are being followed for type 1 tyrosinemia (44 of whom are under 16 years of age), and follow-up is spread over 13 centres, 10 patients are being followed for type 2 tyrosinemia (5 under 16 years of age), with follow-up spread over 9 centres, and 13 with type III tyrosinemia (6 under 16 years of age), with follow-up spread over 6 centres. With regard to current dietary practices, all the centres that responded (12/12 for HTI, 7/9 for HTII and 5/6 for HTIII) use a system of portions of 1g of protein (for milk/cereals and for manufactured foods). The upper protein level (g/100g) used to define when fruit and vegetables are calculated/measured in the dietary treatment of HT was >1g/100g for most of the responding centres. A consensus was reached for dietary management using Delphi principals after 5 consensus meetings: 14/14 voted for same dietary principals for HT I, II and III, 14/14 centres agreed to use 1g protein exchanges for all foods except fruit and vegetables. In addition, 12/14 centres agreed to use phenylalanine analysis rather than protein content for fruit and vegetables. In addition thanks to an almost perfect correlation between phenylalanine and tyrosine (mg/100g protein), the same dietary system for fruit and vegetables as that used for PKU was used. Sharing international dietary analysis allows greater variety in diet. However, a comprehensive international data base for dietary analysis of protein/ amino acids is required

Main references:

Bremer et al 1996
First Supplement The Composition of Foods, McCance and Widdowson 1980
Daly A et al. *Nutrients* 2022
USDA U S Agricultural Research Service (Nutrient data laboratory) and food composition

Dr. Mehmet Cihan Balcı

Paediatric Metabolician,
Istanbul University Medical School, TR

Dr. Mehmet Cihan Balcı was born in Istanbul, Turkey. He obtained his medical degree at Istanbul University, Cerrahpaşa Medical Faculty in Istanbul and completed his pediatric residency training at Istanbul University, Istanbul Medical Faculty Children's Hospital. He trained as a fellow in inborn errors of metabolism at the Istanbul University. He holds a doctorate in nutrition from the Institute of Health Sciences, Istanbul Medical Faculty. He is currently pursuing an on-line master's degree in neurometabolism at the University of Barcelona.

Dr. Mehmet Cihan Balcı has twelve years' experience in inborn errors of metabolism, with special interest in fatty acid oxidation disorders, organic acidurias and neuro-metabolic diseases. He is currently a faculty member at Istanbul Medical Faculty, Department of Child Metabolism and Nutrition. Dr. Balcı resides in Istanbul, with his family.

7. Evaluation of metabolic syndrome and obesity in patient groups with organic acidaemia, MSUD and urea cycle Disorders

Dr. Mehmet Cihan Balcı recalled that dietary interventions in the treatment of inherited amino acid metabolism disorders like organic acidaemia, MSUD and Urea cycle Disorders consits of a restriction of natural protein intake, the administration of synthetic amino acid mixtures and the consumption of special low-protein dietary products. Diet is important to achieve good metabolic control and to prevent neurological complications. As with all children, the aim of the diet is also to promote normal growth and maintain normal body composition. However, such diets with higher intakes of calories, carbohydrates and fats are potentially at risk of inducing higher rates of obesity than those of the general population.

A prospective, observational and descriptive study was carried at Istanbul Medical Faculty, from october 2021 to may 2022, in patients with amino acid metabolism disorders (MMA/PA, UCD/MSUD) undergoing nutritional therapy for at least 2 years, with the aim to evaluate body composition, nutrient intake and markers of metabolic syndrome, to identify potential risks for non-communicable diseases and, to provide recommendations to avoid the development of non-communicable diseases.

The following data were collected: anthropometric measurements (height, weight, BMI, waist circumference), bioelectrical impedance measurements (fat mass, lean body mass, waist circumference hip ratio) and a dietary record (3 days). Biochemical and metabolical tests were also performed (blood sugar, uric acid, albumin, AST, ALT, total cholesterol, HDL cholesterol, LDL cholesterol, triglyceride, hsCRP, HbA1c, plasma insulin level, HOMA index, free carnitine, acylcarnitines).

A number of 116 volunteers were included in the study: 21 patients with MSUD, 32 patients with organic acidurias, 35 with UCD, and 28 healthy controls. BMI values were not significantly different between groups. However, the percentage of obesity was higher in the OA group, but this was not significant. There was a tendency for weight and height measurements (Z-score) to be lower than controls, particularly for height in UCD patients. Regarding BMI, the results obtained in the literature vary, with BMIs sometimes higher than those of the general population, or normal, or even lower. In terms of growth, results have been inconsistent. The explanation could be that pre-pubertal and post-pubertal patients were studied within the same group. Moreover, there are different growth potential, dietary habits, different prevalence of obesity/overweight in societies and variability in nutritional therapies and in the follow-up practices. Bioelectrical impedance analysis didn't find significant differences between the 3 groups. Regarding nutritional records (total amount of protein consumed daily, amount of semi-synthetic amino acid mixture, amount of amino acid mixture consumed per kilogram) UCD and OA groups were similar and lower than MSUD group. However, total protein/ 100 kcal were similar. With regard to biochemical tests, glucose, insulin, HOMA-IR, total cholesterol, LDL cholesterol and HDL cholesterol were found to be similar in all groups. Triglycerides were higher in organic acidaemia group. No significant difference in free carnitine levels was described. The total acylcarnitine level was higher in the organic acidemia group. In addition, a positive correlation existed between the C3-carnitines and BMI of patients with organic acidemia. Some data are highlighted in patients with urea cycle deficits: lower z-scores for height, weight, WHR and muscle mass percentage, highest proportion of individuals with low BMI, low levels of albumin and more pronounced signs of malnutrition. This may be explained by a lowest total protein and natural protein intake in this group.

In conclusion, the study showed that the incidence of overweight, obesity and metabolic syndrome is not different in patients with amino acid metabolism disorders (MMA/PA, UCD/MSUD) undergoing nutritional therapy and that there may be a risk of nutritional deficiency (low height z-scores).

These observations highlight the fact that the follow-up of these patients requires regular visits and anthropometric assessment, regular follow-up of patient's general health and nutrition and collaborative decision-making between dietitians and clinicians.
Larger, multicenter, prospective studies in larger patient populations are needed to address this question.

Main references:

de Castro et al. *Nutrients* 2021
Evans et al. *J Pediatr* 2017
Martín-Hernández et al. *J Inherit Metab Dis* 2009
Pena et al. *Orphanet J Rare Dis* 2015
van Hagen et al. *J Inherit Metab* Dis 2004
Wood et al. *Nutrients* 2020
Wilcoxet al. *J Inherit Metab Dis* 2005

Dr. Tanyel Zubarioğlu

Paediatric Metabolician, Istanbul
University-Cerrahpasa, Cerrahpasa Medical School, TR

Tanyel Zubarioğlu, M.D. is currently a specialist in the field of inborn errors of metabolism and she is an Associated Professor at the Division of Pediatric Nutrition and Metabolism of the Department of Child Health and Diseases in the Istanbul University – Cerrahpasa, Cerrahpasa Faculty of Medicine.

Dr. Tanyel Zubarioğlu was awarded her M.D. degree from Ankara University, Faculty of Medicine, Ankara, Turkey in 2007. She received her postgraduate training in Pediatrics at Sisli Etfal Education and Research Hospital in 2012 and finished pediatric metabolism fellowship at Istanbul University-Cerrahpasa in 2017. She became Associated Professor of Pediatric Metabolism at Cerrahpasa Faculty of Medicine, Istanbul University-Cerrahpasa in 2021.

She has been working as a part of an interdisciplinary research group with approximately 10 collaborators. She currently works on neurometabolic disorders, nutritional treatments of aminoacidopathies and oxidative stress in inborn errors of metabolism.

8. The relation between metabolic control and methionine portioning with relaxed fruit/vegetable consumption in patient with classical homocystinuria

Dr. Tanyel Zubarioğlu explained that CBS deficiency is responsible for classic homocystinuria (HCU). Patients exhibit variable findings as neuropsychiatric signs, skeletal system abnormalities, thrombolic events and optic lens dislocation There are several potential underlying mechanisms responsible from the clinical symptomatology and most of them are related with elevated homocysteine which has a high redox potential and is a highly reactive substance. The main goals of treatment are the prevention of HCU related symptoms (for early diagnosed patients by NBS), or the stabilization of clinical findings for late diagnosed patients, and to maintain a normal growth taking into account quality of life. Dr. Zubarioğlu explained the different treatment modalities. After diagnosis, each patient should have and assessment of pyridoxine responsiveness. Patients with non-responsive CBS deficiency are treated with a protein restricted medical diet (in order to control methionine intakes) and betaine. The modalities of the protein restricted medical nutrition are explained: patients have a restriction in natural protein sources (with either low protein diets with gram protein exchanges lists or low methionine diets with methionine portioning exchange lists). Some categories of food (rich in proteins) are prohibited. Methionine-free L-Amino acid supplement (MFAAM) and low protein food are also required. However, the difficulties to adhere to a severely restricted diet are real and most patients experience problems of dietary compliance and quality of life. In parallel with this observation, the introduction of less strict diets (with unrestricted fruits and vegetables) in PKU patients showed that there was no significant impact on metabolic control. Thus, a prospective, single center clinical trial was conducted at Istanbul University in Pediatric Nutrition and Metabolic Department between May 2020 and April 2021, which included patients with proven pyridoxine non-responsive CBS deficiency (pathogenic biallelic mutation in the CBS gene in patients with positive clinical and/or biochemical findings) who were receiving protein restricted medical nutrition therapy based on a gram-protein calculation. The study was conducted during two periods. During period 1 (May 2020 -October 2020), patients were treated with a diet with MFAAM and limited natural protein with gram protein exchange lists and all foods were weighed. During period 2 (November 2020 to April 2021) MFAAM was continued but diet was changed for a methionine portioning exchange list (1 portion= 25 mg methionine (Met)) and a free food list was provided to the patients (foods containing less than 0,005 g Met/100 g). Met and protein exchange lists were calculated using the United State Department of Agriculture (USDA) database. A face-to-face meeting or online training via WhatsApp or Zoom was given for the nutritional education when switching to Period 2. No changes were made in the principles of follow-up including targeted plasma tHcy levels, and recommended sampling frequency between two periods. Dietary compliance was assessed during both periods, with a questionnaire. Ten patients could be included, with a mean age of 15.8 ± 9.29 years and a mean follow-up of 9.25±7.33 years. Only one patient was non symptomatic, thanks to early diagnosis. During the study, switching to the Met portion exchange list did not result in a statistically significant difference in patients' height z score, body weight z score, and body mass index. Dietary relaxation in Period 2 was not considered to cause a negative effect on metabolic outcome. There was even a trend towards lower rates of tHcy, but this was not significant in this small population. In four patients, betaine treatment was discontinued as metabolic control could be achieved with dietary treatment alone. Statistical difference was noted in all questions of the survey in regard to the dietary compliance, in the sense of improving compliance.

In conclusion, the author concluded that, by switching Met portioning, metabolic control can be achieved and that the liberalization of the diet by a free food list seems to be safe and has no negative effect on metabolic control. Moreover, patients' dietary adherence and compliance improved significantly, and all patients preferred to continue with the new exchange system. The limitations of the study are the small sample size and a relatively short follow-up period.

Main references:

Adam et al. *Mol Genet and Metab* 2013
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