

4th International Symposium on Urea Cycle Disorders

Catalysing new therapeutic approaches

This international symposium has been organised by the Urea Cycle Disorders Consortium (UCDC), the European Registry and Network for Intoxication Type Metabolic Diseases (E-IMD) and the National Urea Cycle Disorders Foundation (NUCDF) and was held on 1-2 September 2012 as an official satellite meeting at the 12th International Congress of Inborn Errors of Metabolism (ICIM) in Barcelona, Spain.

The programme was divided into four sessions focusing on

- (1) pathophysiology,
- (2) early detection and new treatment principles,
- (3) longitudinal studies around the world, and
- (4) clinical themes and patient outcomes.

Summary

The 4th satellite meeting showed that current research on urea cycle disorders is now performed by transnational and collaborative teams within a highly active international network for urea cycle disorders including patient advocacy groups, metabolic experts, basic scientists, psychologists, dieticians, and industry. This is a unique chance to understand the natural history and underlying pathomechanisms of these diseases, to evaluate and improve current diagnostic and therapeutic strategies, and to establish new therapies. This shall help to improve the health of patients with these rare metabolic disorders in the long term.

Dr Roger Butterworth (Montreal, Canada) provided a detailed insight in the recent pathophysiologic understanding of urea cycle disorders focusing on the toxicity of ammonia and glutamine. The role of plasma glutamine levels on the neurological outcome of patients with urea cycle disorders was later (final session) discussed by **Dr Uta Lichter-Konecki** (Washington DC, USA), whereas **Dr Andrea Gropman** (Washington DC, USA) focused on cerebral glutamine concentrations as one of the major biomarkers to be tested and quantified within MRI/MRS studies. Whereas plasma and cerebral ammonia and glutamine concentrations are increased, arginine levels are low in patients with urea cycle disorders (except for hyperargininemia). The arginine-producing enzyme of the human body is argininosuccinate lyase.

Dr Sandesh Nagamani (Houston, USA) demonstrated that this enzyme has another important role in metabolism, i.e. contributing to the synthesis of nitric oxide (NO). He provided convincing evidence that mutated argininosuccinate lyase protein resulted in dysfunction of systematic NO synthesis, since only intact argininosuccinate lyase forms a supercomplex with endothelial NO synthase and argininosuccinate synthetase. This has widespread consequences for the pathophysiologic understanding and treatment of patients with argininosuccinic aciduria.

Dr Vicente Rubio (Valencia, Spain) continued with an overview on new discoveries on urea cycle disorders mostly focusing on carbamylphosphate I and D¹-pyrroline-5-carboxylate synthetase, an enzyme located in the interface of glutamate, proline, and ornithine metabolism. In the second session, **Dr Dietrich Matern** (Minneapolis, USA) gave an overview of recent progress in the development of strategies for implementation of urea cycle disorders in newborn screening programmes in the USA. Using data mining strategies, a combination of parameters has been elucidated that allows early detection of newborns with these diseases. This is in contrast to European countries which mostly do not screen for urea cycle disorders. Comparative and collaborative data analysis would be indispensable to evaluate the impact of early diagnosis and treatment intervention on the outcome for children with these diseases.

New therapies have been discussed by **Dr Patrick McKiernan** (Birmingham, UK), **Dr Ian Alexander** (Melbourne, Australia), and **Dr Philip Gregory** (Richmond, USA). Whereas (cadaveric or living donor) liver transplantation is increasingly used for long-term treatment of patients with urea cycle disorders and shows promising outcome results, other new therapies are still under investigation in clinical studies (e.g. liver cell transplantation)

or in in vitro and in vivo studies (e.g. AAV vector-based gene therapy and in vivo genome editing with zinc finger nucleases). The latter strategies are exciting new approaches to long-term correction of the inherited deficiency underlying urea cycle disorders, however, they need to be further investigated in animals and, if safe and effective, in clinical trials.

In the third session, **Dr Fumio Endo** (Kumamoto, Japan), **Dr Stefan Kölker** (Heidelberg, Germany), and **Dr Marshall Summar** (Washington DC, USA) demonstrated results on patient registries and longitudinal outcome studies from Japan, Europe, and the USA.

More than 1,000 patients with urea cycle disorders (i.e. approximately, 200 from Japan, 350 from Europe, and 600 from USA) have been enrolled to these studies worldwide during the last years. This large systematic data collection is the basis for deep and comparative phenotyping, epidemiological research, evaluation of currently available diagnostic and therapeutic strategies, and identification of knowledge gaps. These studies will have a significant impact on improving the knowledge base of these rare diseases and shall help harmonising current discrepancies in acute and long-term management.

In the final session, **Dr Renata Gallagher** (Denver, USA) shifted the focus on the manifestation of hepatic involvement in patients with urea cycle disorders, in particular the manifestation of acute liver failure and the long-term risk for developing liver carcinoma. For some patients, hepatic problems might be more pronounced than neurological problems and thus are important to identify early. **Dr Avihu Boneh** (Melbourne, Australia) discussed the controversial topic on approaches to dietary treatment. He showed that (excessive) protein restriction in the acute metabolic decompensation might have many negative effects and, therefore, daily protein requirements should be carefully calculated to reduce the burden of ammonia and glutamine toxicity on the one hand, and to provide a sufficient basis for protein biosynthesis on the other hand. **Dr Susan Waisbren** (Boston, USA) and **Peter Burgard** (Heidelberg, Germany) presented results on neuropsychological outcomes, quality of life and behavioral abnormalities of UCDC and E-IMD study patients. They demonstrated the significant burden of impaired neurocognitive functions and based on this reduced quality of life and behavioral abnormalities in many patients with urea cycle disorders. Careful evaluation of these parameters is extremely important for a holistic approach to individual patients and for tailoring of care concepts.

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