Journal of Pediatric Biochemistry 4 (2014) 1–3
DOI 10.3233/JPB-140099
IOS Press

Guest Editorial

Urea cycle disorders revisited – clinical, biochemical and therapeutical aspects

Johannes Häberle*
Division of Metabolism, University Children's Hospital, Switzerland and Children's Research Center, Zurich, Switzerland

Urea cycle disorders (UCDs) are inherited defects of nitrogen metabolism that can result in life-threatening hyperammonemia and severe neurological disease [1]. The overall incidence of the entire group of disorders is estimated at about 1 in 35.000 to 40.000 [2, 3] but there may still be underreporting due to undiagnosed patients. The affected pathway, the urea cycle, is only expressed in the liver and is the main route for detoxification of ammonia in the human body [4]. There are six enzymes and two transporters directly involved in this pathway but, in addition, several inherited and acquired conditions can lead to impaired urea cycle function. Accordingly, there is a long list of differential diagnoses that can result in primary or secondary hyperammonemia, i.e. direct or indirect defects of the urea cycle [5]. UCDs are panethnic diseases but the distribution of disorders around the world is heterogeneous resulting in different frequencies of single UCDs in Japan, Europe or the US.

More than 80 years ago, the urea cycle was first described by Krebs and his doctoral candidate Henseleit who nicely brought together at that time knowledge on ureagenesis with the presence of arginase in liver of mammals but not birds, and who elucidated the other amino acids involved in the urea synthesis reaction [6]. Remarkably, already when first reporting urea synthesis in man, the authors correctly identified the liver as the only organ where this can take place. The first defect of the urea cycle, identified based on abnormal amino acid excretion in urine, was described 26 years later in two children with epilepsy, ataxia, friable hair and severe mental retardation [7]. Since then, patients affected by any of the enzymes and transporters involved have been identified all over the world, all genes have been cloned, diagnostic analyses were refined, animal models were developed and novel treatment strategies were suggested.

Currently, diagnosis of UCDs relies on investigation of metabolites including plasma ammonia and amino acids as well as urine orotic acid and organic acid analysis. Confirmation of a suspected UCD generally requires mutation analysis which, in addition, provides the basis for family counselling and prenatal testing. Management of UCDs is based on low-protein diet, drugs allowing for alternative nitrogen excretion and amino acid supplementation, the latter in order to avoid essential amino acid deficiencies and to support residual urea cycle function. For both, diagnosis as well as acute and long term treatment, there are guidelines in use in many countries that still are not entirely identical but that only have some differences regarding few aspects [8–10]. With the initiation of national, international and even intercontinental networks and registries for UCDs, already existing for some years in the US [11] and more recently established also in Europe [12] and Japan, and with the expressed intention to collaborate between these networks, it seems likely that the expected broader knowledge base will lead to joint and improved management strategies to the benefit of UCD patients.

As a visible sign of the growing together of the UCD communities, this present Special Issue of the

*Corresponding author: Johannes Häberle, University Children's Hospital Zurich Division of Metabolism, 8032 Zurich, Switzerland. Tel.: +41 44 266 7342; Fax: +41 44 266 7167; E-mail: Johannes.Haeberle@kispi.uzh.ch.

Journal of Pediatric Biochemistry can serve. The reader will find contributions from leading experts from many different centers (almost) all over the world including from India and the US. This Special Issue will provide information on UCDs from a clinical, diagnostic, biochemical and therapeutic perspective and is thus a colorful picture of this group of rare inherited metabolic diseases.

The first two articles describe the clinical situation in two different settings. Staufner and colleagues from Heidelberg, Germany, present the history of ornithine transcarbamylase deficiency, the most common UCD, in one family and hereby illustrate the typical variable phenotype in this disorder. Moreover, the biochemical hallmarks are discussed. The paper by Jalan and coworkers from Mumbai, India, provides an extremely important insight into the management of UCDs as an example for rare diseases in general in a developing country. This is done by in detail description of the situation including the many daily problems that health care professionals and families are facing and is complemented by several suggestions for advancement of the current management aiming for an improvement of the outcome of UCDs in developing countries.

Following these clinical articles, there are several contributions dealing with various diagnostic and biochemical issues. Claude Bachmann, Professor emeritus from Lausanne, Switzerland, focuses on preanalytical aspects that are important in order to achieve the right diagnosis if UCDs are suspected. This is done not only by explaining the correct procedure but also by relating the preanalytical effects to the medical decisions that need subsequently to be made. This is followed by two state-of-the-art articles, the first of which by Gautschi and colleagues from Bern, Switzerland, who elaborate on the extensive experience that their laboratory has gained over many decades of measuring urea cycle enzymes. Their important message is clear: there is still a place for enzymatic analysis in selected UCD patients and situations. Therefore, enzyme analysis plays a complementary role to mutation analysis, and this is in detail described and discussed in the article by Rüfenacht and Häberle from Zurich, Switzerland. Their paper gives a historical perspective to genetic testing for all UCDs, explains the advantages and limitations of currently used methods and provides an outlook to future prospects of sequencing analysis.

Next in this issue, the reader will find a contribution by Martinelli from Rome, Italy, describing the most common conditions affecting urea cycle function in a secondary way. The author explains in detail the metabolic changes encountered in the various disorders illustrating hereby the close interrelation of the urea cycle with other pathways.

This Special Issue concludes with two papers that are at the edge between current practice and future perspectives. Ah Mew and colleagues from Washington and Philadelphia, USA, review the development of stable isotopes for investigations into nitrogen metabolism. They convincingly describe the use of stable isotopes not only for measuring hepatic ureagenesis as a tool to detail the phenotypic severity but also as a method for evaluation of the efficacy of novel treatment strategies in UCD patients. Finally, Viecelli and Thöny from Zurich, Switzerland, give a thorough picture of the current status of gene therapeutic approaches for UCDs by reviewing available animal models, gene therapy trials, pre-clinical studies but also by explaining experimental procedures. Overall, they provide a full description on the challenges of this field of novel therapy.

In summary, this Special Issue on UCDs will be of value for the interested non-expert as well as for the knowledgeable expert. In addition, it is hoped that one achievement of this series of articles on a group of rare diseases will be the increased awareness of healthcare professionals because only by early considering UCDs as possible differential diagnosis in any patient with unexplained change in consciousness, the chances of an early diagnosis will improve as will, hereby, the prognosis of affected patients.

References

[1] Brusilow S, Horwich A. Urea cycle enzymes. In: Scriver C, Beaudet A, Sly W, Valle D (eds) The metabolic & molecular bases of inherited disease, 8th edn. McGraw-Hill, New York, 2001; pp 1909-1963.

[2] Summar ML, Koelker S, Freedenberg D, Le Mons C, Häberle J, Lee HS et al. The incidence of urea cycle disorders. Mol Genet Metab 2013; 110(1-2): 179-80.

[3] Wilcken B, Haas M, Joy P, Wiley V, Bowling F, Carpenter K et al. Expanded newborn screening: outcome in screened and unscreened patients at age 6 years. Pediatrics 2009; 124(2): e241-8.

[4] Häussinger D. Nitrogen metabolism in liver: structural and functional organization and physiological relevance. Biochem J 1990; 267(2): 281-90.

[5] Häberle J. Clinical and biochemical aspects of primary and secondary hyperammonemic disorders. Arch Biochem Biophys 2013; 536: 101-8.

[6] Krebs H, Henseleit K. Untersuchungen über die Harnstoffbildung im Tierkörper. Hoppe-Seyler's Zeitschrift für

Physiologische. Chemie 1932; 210: 33-66.
[7] Allan JD, Cusworth DC, Dent CE, Wilson VK. A disease, probably hereditary characterised by severe mental deficiency and a constant gross abnormality of aminoacid metabolism. Lancet 1958; 1(7013): 182-7.
[8] Häberle J, Boddaert N, Burlina A, Chakrapani A, Dixon M, Huemer M et al. Suggested Guidelines For The Diagnosis And Management Of Urea Cycle Disorders. Orphanet J Rare Dis 2012; 7: 32.
[9] Lanpher BC, Gropman A, Chapman KA, Lichter-Konecki U, Urea Cycle Disorders C, Summar ML (updated in 2011). Urea Cycle Disorders Overview. In: Pagon RA, Adam MP, Bird TD (eds) Gene reviews, 2010/03/20 edn, Seattle.
[10] Summar M. Current strategies for the management of neonatal urea cycle disorders. J Pediatr 2001; 138(1 Suppl): S30-9.
[11] Tuchman M, Lee B, Lichter-Konecki U, Summar ML, Yudkoff M, Cederbaum SD et al. Cross-sectional multicenter study of patients with urea cycle disorders in the United States. Mol Genet Metab 2008; 94(4): 397-402A.
[12] Kölker S, Dobbelaere D, Chakrapani A, Parker S, Burgard P, Hoffmann G et al. European registry and network for intoxication type metabolic diseases (E-IMD) (Abstract). J Inher Metab Dis 2011; 34: S93.