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## SPECIAL ISSUE

### Current opinion in pediatric metabolic disease

Editor:

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## EDITORIAL

# Current opinion in pediatric metabolic disease

Ertan MAYATEPEK

Metabolic diseases in children are not really common and many paediatricians have only limited experience of them. The presentation is initially often non-specific, which can make the diagnosis difficult. During the last years there has been tremendous progress in the understanding of this group of disorders. However, the large number of different diseases with an increasing number of genetic defects in various biochemical pathways makes it difficult to be familiar with diagnostic strategies, rational therapy and the latest research results. The aim of this special issue is to summarize current knowledge of some representative diseases or groups of disorders of the broad range of pediatric metabolic diseases. In this editorial an overview and short summary of the different topics included in this special issue is given.

The review of Häberle concentrates on urea cycle disorders. They comprise a group of inherited defects of metabolism affecting the detoxification of excess nitrogen and, hereby, leading to hyperammonemia which is primarily toxic to the central nervous system. The urea cycle is located in the liver and consists of six consecutive enzymatic steps. Enzymatic deficiencies are known in all of them. The clinical presentation of urea cycle defects comprises a broad range of clinical symptoms and can manifest in neonates but also in older children and adolescents. Hyperammonemia is the leading biochemical parameter for diagnosis. To confirm diagnosis a variety of biochemical, enzymatic and genetic tests exist. Most patients require a strict dietary protein restriction, nitrogen scavenger drugs and amino acid supplementation. Liver transplantation might be a therapeutical option, at least in some patients. In general, patients with urea cycle defects are still affected by a poor outcome. Quality of life also

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depends on an increased awareness of these disorders and expertise as well as collaboration of all medical professionals.

The most common cause of persistent hypoglycaemia in infancy represents congenital hyperinsulinism. In their review Marquard and colleagues point out that this is biochemically characterized by an upregulated secretion of insulin from pancreatic beta cells in relation to blood glucose concentration. Up to now, eight different genes are described in relation to this disease. Nevertheless, in still up 50% of patients the genetic basis remains unknown. The clinical presentation is heterogenous with regard to age of onset, severity and symptoms. During the last years, substantial progress has been made, mainly by  $^{18}\text{F}$ -L-dopa positron emission tomography for differentiating diffuse and focal disease. Treatment in diffuse forms includes mainly attempts with diazoxide and octreotide. In patients with the focal form a limited pancreatectomy can lead to the cure of

the disease. Adequate patient's management also requires a highly experienced team in diagnostic work-up and treatment.

A translational approach to an enigmatic disease is presented with glutaric aciduria type I by Boy and colleagues. This disease is due to an enzymatic block in the metabolism of L-lysine, L-tryptophan and L-hydroxylysine. Biochemically it is characterized by accumulation of putatively toxic glutaric and 3-hydroxyglutaric acid. It manifests often after an acute encephalopathic crisis with a complex movement disorder with predominant dystonia superimposed on axial hypotonia. Newborn screening allowing neonatal identification of asymptomatic patients by tandem mass spectrometry with subsequent metabolic treatment has significantly improved the neurological outcome. Post mortem studies and investigations in glutaryl CoA dehydrogenase-deficient mice have dramatically helped to unravel the pathomechanism. It is illustrated that a translational approach to this disease is indispensable to further elucidate major principles of neuroprotective strategies.

Biosynthesis of bile acids, which are formed from cholesterol in the liver, play an important role as biological detergents and as metabolic regulators of lipid, glucose, and energy homeostasis. Several enzymatic steps are involved in the biosynthesis of bile acids. Genetic defects in the enzymes involved in the biosynthesis result in an accumulation of atypical bile acids or intermediates. These defects can cause liver diseases varying from mild to severe clinical symptoms. In this issue, Herebian and myself review the most known inborn errors in bile acid metabolism and their mass spectrometric confirmation in biological fluids.

Mitochondrial diseases in children constitute a diagnostic and therapeutic challenge for the clinician. Although research is ongoing, there is actually no cure for these disorders and prognosis remains poor. Isolated malfunction of the first oxidative phosphorylation (OXPHOS) complex (complex I) is the most frequently observed defect. It may manifest itself as Leigh syndrome, which is an early-onset neurodegenerative disease with a very poor prognosis. Distelmaier and colleagues present in their review cell biological consequences of Leigh

syndrome and give a brief overview of recent new findings.

The most common disorder of the gamma-glutamyl cycle is glutathione synthetase deficiency. All relevant aspects of this disorder are reviewed by Schlune and myself. This metabolic disease is characterized by decreased levels of cellular glutathione and 5-oxoprolinuria. Based on the severity of the clinical symptoms it is classified into three groups with mildly, moderately or severely affected patients. The most severe form is mainly associated with metabolic acidosis, haemolytic anemia and central nervous system damage. Diagnostic and therapeutic options are discussed in detail.

Canavan disease is a genetic neurometabolic disease caused by mutations in the *ASPA* gene. Important clinical features include beside others macrocephaly, hypotonia, head lag and developmental delay. Heterogeneity of the clinical phenotype, diagnostic findings, treatment aspects as well as recent research results are reviewed and presented by Lienhard and Sass.

New therapeutic options and progress of approved therapies have made lysosomal storage diseases one of the most exciting group of metabolic diseases. Hoffmann and myself summarize current achievements in disorders like Gaucher disease, Fabry disease, Mucopolysaccharidosis type I, II, and IV, Pompe disease, and Niemann-Pick disease type C and give an outlook towards present and future treatment options (e.g. enzyme replacement therapy, substrate reduction, bone marrow or stem cell transplantation, pharmaceutical chaperones).

It is intended and hoped that the collection of articles on representative pediatric metabolic diseases in this special issue of the Journal of Pediatric Sciences will stimulate discussion, collaboration, and research, which ultimately will lead to further improved diagnosis, management, and outcome, in patients with these inborn errors of metabolism.