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EDITORIAL

Editorial

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This special edition of the *Journal of Inherited Metabolic Disease* focuses on the diagnosis, disease course and treatment of adults with IMDs.

Management of adults with IMDs presents several challenges. First, it is important to recognise that the phenotypic spectrum seen in any disease may differ from that described in children; Saudubray and Mochel discuss the possible mechanisms underlying this phenotypic variability with focus on genetic, environmental and ontogenic factors and the effects of ageing. The use of whole exome and genome sequencing which over the last years has found its way into routine clinical care has broadened our understanding of the spectrum of phenotypes. This is nicely illustrated by van Dijk et al., who describe a mild case of pontocerebellar hypoplasia, diagnosed at the age of 23 years.

As the clinical features of IMDs evolve with age, so the clinical management must change as well. In general, patients with disorders of intermediary metabolism who survive childhood are at less risk of severe decompensation in adulthood, but instead develop new and chronic complications. This is highlighted in the study by Kolker et al., who describe progressive (multi-)organ dysfunction in adolescents and adults with organic acidurias following early diagnosis and treatment, even in individuals considered to be "metabolically stable".

There are also IMDs which primarily affect adults. Acute intermittent porphyria rarely presents in childhood but leads to a high, persistent burden of disease in adult patients separate to their recurrent attacks, as described by Neeleman et al. Most patients develop hypertension and renal failure, which contribute to the high costs of medical care for this group of patients.

Long-term complications in disorders that do not carry a risk of acute decompensation may also seriously impact patients' lives. Regenboog et al. describe the incidence of hepatocellular carcinoma in a series of patients with Gaucher disease and recommend screening during follow-up. Problems with skeletal development during childhood also result in a high burden of disease in adults. This is well recognised in the mucopolysacharidoses, as described by van Oussoren for Mucolipidosis type III, but is also true in inherited metabolic bone disease. Chesher et al. describe the phenotype of adults with X-linked hypophosphatemia (XLH) who also face lifelong skeletal complications requiring multiple surgical interventions. Fortunately, the outlook for XLH patients may be better when treatment is initiated early.

Another important challenge is dealing with pregnancy and fertility issues. Well known examples are infertility in classical galactosaemia, teratogenicity in PKU and the risk of maternal metabolic decompensation in OTC deficiency, but similar concerns exist for other conditions. Kuseyri et al. describe a series of pregnancies in patients with tetrahydrobiopterin disorders. Outcomes were good for 16 pregnancies in 7 patients but they make a case for intensive clinical and biochemical supervision. This approach is essential for all IMDs if we are to expand our knowledge of pregnancy outcomes.

Ovarian insufficiency in classical galactosaemia remains an unsolved problem: two thirds of girls with classical galactosaemia achieve spontaneous menarche, but few cycle regularly into adulthood, as described by Frederich et al., and we need to be able to offer women who wish to start a family options other than natural conception. Haskovic and coworkers consider the technical and ethical issues involved in offering intrafamilial oocyte donation to galactosaemic patients.

Moving to the theme of treatment of adults with IMD, one of the main challenges is timing of therapeutic intervention; in attenuated forms of disease, which are prevalent in adults, the right moment to start treatment is often unclear. Much depends on the extent to which pathology and disease manifestations may be reversible. Can we wait until signs and symptoms

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have appeared, or should we initiate therapy as soon as possible in an attempt to prevent irreversible damage? If it is not possible to reverse or prevent disease, is delaying onset or slowing progression a worthwhile outcome?

When treating patients with cerebrotendinous xanthomatosis (CTX) with chenodeoxycholic acid, it seems to be crucial to start as soon as possible. Amador et al. show that delayed treatment cannot halt disease progression, while early intervention may improve symptoms. Better awareness and earlier diagnosis of CTX is thus essential.

The window of opportunity for treatment of Niemann Pick B patients is probably wider; adults tend to have relatively stable disease and, as in Gaucher disease, may still have reversible disease after many years. In an open-label study, Wasserstein and colleagues describe the beneficial effects of Olipudase Alfa (recombinant acid sphingomyelinase) for treatment of adults with acid sphingomyelinase deficiency. They show very promising effects, including improvements in lung diffusing capacity of 35%.

Dietary interventions are an essential part of the treatment of many IMDs, and they continue to develop. Schifmann and co-workers report that triheptanoin treatment was safe as a therapeutic agent in adult polyglucosan body disease, but they were not able to establish any clinically relevant effects. This illustrates the challenges involved in investigating a potential new treatment for a rare disease in a heterogeneous cohort of adult patients where the natural history is not well characterised. Hayasaka and colleagues show that medium-chain triglyceride supplement therapy with a low-carbohydrate formula can improve ammonia detoxification in hepatic argininosuccinate synthetase and, most likely, glutamine synthase deficiencies.

Last but not least, Sirrs and colleagues describe the use of solid organ or bone marrow transplantation as disease modifying therapy in adults with IMDs. They argue that transplantation should be used for the same diseases in adults as in children, but lack of awareness of these diseases in the adult transplant setting limit access to transplantation, and age-related prognostic factors may disadvantage adult patients.

This special edition of JIMD shows the breadth of work which is currently going on in the adult IMD world aimed at describing the special aspects of IMD in this large patient population. The editors and authors hope that a better understanding of the clinical features and treatment challenges should help to improve the care of adults with IMDs.