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EDITORIAL

Guidelines on homocystinurias and methylation defects: a harmonized approach to diagnosis and management

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Inborn errors of metabolism of homocysteine, folate, cobalamin, and methylation belong to the most intriguing metabolic disorders and link metabolism to organ- and neurodevelopment and regulation of gene expression on levels we are just beginning to understand. The European Network and Registry for Homocystinurias and Methylation Defects (E-HOD) consortium (for more information, see http://www.e-hod.org) created three excellent state-of-the-art recommendation papers reviewing clinical spectrum, diagnosis, and treatment of this group of disorders (see Huemer et al., 2016, Barić et al., 2016, and Morris et al., 2016 this issue).

Inherited methylation disorders are probably largely underdiagnosed disorders. They can primarily affect liver, brain, and muscle function in various combinations, but their clinical presentation can vary considerably. Although some patients were recognized in the past by newborn screening (NBS), or sometimes by serendipity, — mostly based on high methionine levels —, no clear recommendations have been offered up till now for follow-up and dietary therapy. Barić et al., 2016 present the first consensus reference for diagnosing and managing methylation disorders, including suggestions on low-methionine diet, based on expertise recommendation and a thorough literature review (Barić et al., 2016, this issue).

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Cobalamin metabolism defects are an emerging group of multisystem disorders. There is a a very intensive discussion between clinicians and scientists with regards to proper management (Morava et al. 2015). Cobalamin C (cblC) defect has been managed in the past with dietary protein restriction, oral carnitine supplementation, betaine, and MI hydroxocobalamin therapy. However, many patients have developed progressive neurologic deterioration and eye disease often causing blindness, even when fully compliant with the recommended therapy. Recent observations suggested that management practices must be re-evaluated.

Huemer et al. (2016) (this issue) conclude that there is no evidence for a beneficiary effect of dietary restriction and carnitine supplementation in cblC patients. The paper raises the timely question on the efficacy of hydroxocobalamine treatment with dose escalation. The authors recommend using a daily IM dose of 0.3 mg/kg hydroxocobalamin therapy throughout the disease course. Although long-term evidence for the clinical benefit of dose escalation is not yet available, harmonizing our clinical approach will definitely help inform improved therapeutic guidelines in this devastating condition. Additionally, liberalizing the diet in cobalamin and other remethylation defects will improve the quality for life for many patients.

Finally, and very importantly, the third review and guideline paper by Morris et al. (2016) (this issue) focuses on classic homocystinuria due to cystathione beta synthase (CBS) deficiency. This disorder is definitely underdiagnosed due to high clinical variability, later-onset of symptoms in pyridoxine-sensitive CBS defect, metabolic differences between pyridoxine-sensitive and nonsensitive forms, and our current NBS practices (Huemer et al., 2015). Patients with the non-pyridoxine-sensitive form benefit of the methionine-restricted diet, which is, however, extremely hard to maintain

later in life, resulting in poor compliance. The pyridoxine-responsive form of the disease is way much easier to treat, and so early or —optimally— presymptomatic diagnosis is crucial. The sensitivity of the current NBS method for detecting this latter form is largely unknown and probably very low. The authors conclude that the NBS sensitivity may be increased by selecting cutoff values as low as possible for Met and Met/Phe ratios. Little experience is yet available regarding the use of total homocysteine (tHcy) in NBS. The authors also emphasize the importance of selective screening in any patient with skeletal ophthalmologic, vascular, or central nervous system (CNS) symptoms or psychiatric disease. The paper makes it clear that available data on target homocysteine levels on treatment are rather limited and the authors expect that the E-HOD registry will provide answers in the near future. For the moment, the advice is in pyridoxine-responsive patients to aim for a tHcy <50 μmol/L and in pyridoxine-unresponsive patients <100 μmol/L.

References

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