WHEN TO MEASURE PLASMA HOMOCYSTEINE AND HOW TO PLACE IT IN CONTEXT: THE HOMOCYSTINURIAS

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Abstract
This review presents clinical patterns that should trigger homocysteine measurement in blood, as well as the further diagnostic work-up focused on inborn errors of metabolism and disorders of vitamin B12 (cobalamin) absorption and supply. The numerous conditions (e.g. cardiovascular disease, Alzheimer’s disease) for which mild-to-moderate hyperhomocysteinaemia caused by genetic polymorphisms or acquired reasons is considered a risk factor are beyond the scope of this review.

Homocysteine is a sulphur-containing amino acid, which is derived from the amino acid methionine. Homocysteine is either trans-sulphurated to form cystathionine and then cysteine, or re-methylated to methionine. The trans-sulphuration reaction depends on the enzyme cystathionine beta synthase and its cofactor vitamin B6. The re-methylation reaction not only involves the enzymes methionine synthase and methionine synthase reductase but also depends on the cofactor cobalamin and on the provision of methyl groups from the folate cycle. Because the homocysteine–methionine cycle provides for the vast majority of methyl groups in the body, it is central to numerous pathways that depend on methyl group supply, such as creatine synthesis or DNA methylation. Based on this premise, the severity of clinical presentations of inborn errors of metabolism, such as classical homocystinuria or the cobalamin C (cblC) defect, affecting this pathway is unsurprising.

Keywords
re-methylation, cystathionine beta synthase deficiency, MTHFR deficiency, vitamin B12, cobalamin, gastric intrinsic factor, Imerslund-Gräesbeck syndrome, transcobalamin, TCN2

Introduction: Metabolic and Absorption Pathways

Homocysteine (Hcy) is a sulphur-containing amino acid that is derived from the essential amino acid methionine (Met). Met is metabolised by Met-adenosyltransferase (MAT I/III) to S-adenosylmethionine (AdoMet). Multiple methyltransferases are recipients of the methyl groups generated by the next step, the conversion of AdoMet to S-adenosylhomocysteine (AdoHcy). AdoHcy is transformed to Hcy, which is either irreversibly converted to cystathionine and thereafter cysteine by cystathionine beta synthase (CBS) and its cofactor vitamin B6 (the trans-sulphuration pathway) or re-methylated to Met by methionine synthase (MS; coded by the MTR gene), which depends on methionine synthase reductase (MSR; MTRR), the cofactor cobalamin (Cbl; synonym: vitamin B12) and methyl groups from the folate cycle delivered by 5-methyltetrahydrofolate (5-MTHF). Total Hcy (tHcy) in blood is elevated if the trans-sulphuration or the re-methylation pathway is disrupted (1, 2). If trans-sulphuration fails, Hcy is re-methylated to Met in greater amounts. Therefore, the biochemical fingerprint of CBS deficiency or classical homocystinuria is elevated Hcy in the presence of high Met and often low cystathionine (3, 4). Defective re-methylation of Hcy to Met results in both low AdoMet and elevated AdoHcy and thus causes impaired methyl (or ‘one-carbon’) group supply for numerous methylation reactions, e.g. creatine synthesis or DNA methylation, a regulatory mechanism involved in epigenetic processes (2) (Figure 1).

The re-methylation disorders encompass inborn errors that directly affect the enzymes MS (MTR; in the cblG defect) or MSR (MTRR, in the cblE defect), as well as deficiency of methyltetrahydrofolate reductase (MTHFR; MTHFR), in

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which the body is deprived of the methyl group-providing substrate 5-MTHF from the folate cycle. Elevated tHcy (and eventually low Met) is the biochemical fingerprint of the cblE and cblG defects, of MTHFR deficiency and of the cblD-Hcy (MMADHC) defect (5). As Cbl is an essential cofactor in the re-methylation reaction, inborn errors of absorption or intracellular processing of Cbl also cause defective re-methylation. Gastric intrinsic factor (GIF) deficiency, Imerslund-Graesbeck syndrome (AMN; CUBN) and transcobalamin deficiency (TCN2) are inborn disorders of Cbl absorption; and the cblF (LMBRD1), cblJ (ABCD4), cblC (MMACHC) and cblD-MMAHcy (MMADHC) defects impair the shared intracellular processing pathway of Cbl. These conditions affect not only re-methylation but also the intramitochondrial degradation of methylmalonic acid (MMA), to which Cbl is also essential. Elevated tHcy (and eventually low Met) in the presence of high MMA is the biochemical fingerprint of this group of disorders (Figure 2). Severely impaired Cbl supply due to nutritional deprivation or acquired conditions hampering absorption (e.g. pernicious

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**Figure 1.** Simplified methionine-homocysteine pathway. AdoMet, S-adenosylmethionine; AdoHcy, S-adenosylhomocysteine; MTHFR, 5,10-methylenetetrahydrofolate reductase; MS, methionine synthase; CH3-Cbl, methylcobalamin; GNMT, glycine N-methyltransferase; CBS, cystathionine β-synthase; MAT I/III, methionine adenosyltransferase. *methyl group transfer

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**Figure 2.** Simplified overview of the intracellular processing of Cbl and its intracellular metabolites adenosyl-Cbl and methyl-Cbl. In cblF and cblJ disease, liberation of Cbl from the lysosome and processing to the MMACHC gene product (cblC), which decyanides Cbl, fails. Depending on the locus of the mutation in the MMACHD gene, cblD disease may either affect the synthesis of both adenosyl- and methyl-Cbl or of only one of the pathways. Adenosyl-Cbl is the cofactor for intramitochondrial MMA metabolism by mutase and the cblA and cblB proteins. Methyl-Cbl is cofactor for the remethylation of Hcy to Met by MS (CblG) and MSR (cblE). *Main disorders in this pathway are gastric intrinsic factor deficiency (GIF), Imerslund Graesbeck syndrome (AMN; CUBN) and transcobalamin deficiency (TCN2).
anaemia) also deprive the pathways of both adenosyl- and methyl-Cbl and can mimic the clinical and biochemical presentation of inborn errors of Cbl metabolism (Table 1) (6–8).

Clinical Situations That Should Prompt Measurement of tHcy: The Natural History

The clinical presentation of the homocystinurias is widespread in two dimensions. One is age – although the majority of patients come to clinical attention as neonates or infants, homocystinurias may present any time throughout life. The second dimension is the clinical presentation –

Table 1. Inborn errors and acquired conditions associated with elevated tHcy in blood

| Gene | MIM code | MMA | Cbl |
|------|----------|-----|-----|
| CBS deficiency (classical homocystinuria) | CBS 236200 | n | * |
| Acquired conditions resulting in decreased cobalamin supply/absorption |
| *Nutritional Cbl deficiency including neonatal due to maternal Cbl deficiency | - | - | ↑ ↓ |
| *IF gastric parietal cell antibodies | - | - | ↑ ↓ |
| *Gastric intrinsic factor deficiency | GIF 261000 | ↑ often ↓ |

Inborn errors of cobalamin absorption

| Syndrome | Gene | MIM code |
|----------|------|----------|
| *Imerslund-Gräsbeck syndrome | AMN 261100 | ↑ often ↓ |
| *Transcobalamin deficiency | TCN2 275350 | ↑ |

Combined inborn errors of remethylation

| Gene | MIM code | MMA |
|------|----------|-----|
| *cbldefect | LMBRD1 277380 | ↑ * |
| *cblJ defect | ABCD4 614857 | ↑ * |
| *cblC defect | MMACHC 277400 | ↑ * |
| *cblD-MMAHcy defect | MMADHC 277410 | ↑ * |

Isolated inborn errors of remethylation

| Gene | MIM code | MMA |
|------|----------|-----|
| *cblD-Hcy defect | MMADHC 277410 | n * |
| *cblE defect | MTR 236270 | n * |
| *cblG defect | MTHFR 250940 | n * |
| *MTHFR deficiency | MTHFR 236250 | n * |

*low or normal methionine; *high methionine; *Cbl is expected to be normal (but may be affected by acquired conditions such as decreased supply). In haptocorrin deficiency, transcobalamin receptor deficiency, MTHFD1 deficiency, and the X-chromosomally inherited HCF1 defect, tHcy may be but is not consistently elevated. In hypermethioninemia caused by MAT I/II, GNMT, SAHH or ADK deficiencies, tHcy is usually normal or only mildly elevated (usually below 50 μmol/L) (6, 19, 20).

Homocystinurias are clinically heterogeneous, multi-system disorders. Homocystinurias should be considered as a differential diagnosis in a neonate with acidosis, failure to thrive, neutropenia, seizures and irritability; in a child with cognitive impairment, lens dislocation and a marfanoid habitus; in an adolescent with atypical haemolytic-uraemic syndrome and acute renal failure; or in an adult with psychiatric symptoms, dementia, subacute combined degeneration of the spinal cord and signs of peripheral neuropathy or thromboembolism (7, 9–11).

Acquired re-methylation impairment due to insufficient Cbl supply should be suspected in any infant developing symptoms of neurocognitive decline, eventually microcephaly, feeding difficulties, failure to thrive and irritability, typically in the second-to-third quarter of the first year. As the only natural Cbl sources for humans are animal products, the offspring of breastfeeding mothers adhering to a vegan lifestyle are especially prone to nutritional Cbl deficiency. Long-standing Cbl deficiency in an infant is a serious condition that may cause irreversible neurological damage (7, 12, 13).

The homocystinurias share the hallmark of damage to the central nervous system. Feeding difficulties, failure to thrive, irritability, seizures, cognitive impairment, movement disorders, neuropathy, white matter disease and hypomyelination, as well as combined degeneration of the spinal cord, should alert the clinician to re-methylation disorders. Early-onset (before Month 12 of life) Cbl-related inborn errors of re-methylation (especially the most frequent cblC defect) often also cause retinopathy (retinitis pigmentosa) and optic atrophy, resulting in a decline of visual acuity and even blindness. This specific eye damage does not occur in patients with MTHFR deficiency or in late-onset patients with Cbl-related inborn errors of re-methylation. In all re-methylation defects, children may present with failure to thrive and developmental delay, while in adolescent or adult patients, psychiatric problems, neuropathy and dementia are leading symptoms (5, 14).

Classical homocystinuria patients show intellectual, psychiatric and behavioural problems, as well as movement disorders and sometimes seizures. Their leading eye problem is ectopia lentis, which is predominantly seen in untreated young, severely affected patients (3, 4).

Homocystinurias are in most cases multi-system disorders with a broad range of additional, non-neurological symptoms. A marfanoid skeletal phenotype with excessive height and limb length, arachnodactyly and thromboembolism are characteristic manifestations of CBS deficiency. Clinical liver disease is not a hallmark of CBS deficiency, but fatty liver or liver fibrosis has been noted (3, 4).

In re-methylation disorders, thromboembolism occurs – like in CBS deficiency – mostly in adolescence or adulthood. In contrast to CBS deficiency however, re-methylation disorders...
are also complicated by micro-angiopathy, which may at any age manifest either as chronic glomerular or tubulo-interstitial disease, acute renal failure under the clinical picture of atypical haemolytic-uraemic syndrome, pulmonary arterial hypertension or hydrocephalus (the latter mainly in newborns). Megaloblastic anaemia, neutropenia or pancytopenia is frequent; cardiac malformations and cardiomyopathy occur sometimes, while liver disease is quite rare in re-methylation defects (5, 9, 10, 14). Table 2 displays an overview of the most frequent symptoms of the homocystinurias at different ages (3–5, 9, 10, 14–16).

Table 2. Symptoms at disease presentation by age in remethylation disorders (a) and CBS deficiency (b) in estimated order of frequency. There is wide range of ages at presentation and spectrum of severity, from asymptomatic individuals to severely affected patients with multi-system disease.

(a) Remethylation disorders

Early onset (<12 months)
- Feeding difficulties / failure to thrive
- Muscular hypotonia
- Developmental / cognitive impairment
- Seizures
- Eye disease (nystagmus, visual impairment)*
- Hydrocephalus
- Acute metabolic decompensation
- Cardiac disease (cardiac malformation; cardiomyopathy
- Atypical haemolytic uraemic syndrome
- Behavioural problems
- Movement disorders
- Stroke / thromboembolic event
- Anaemia/thrombocytopenia or pancytopenia, megaloblastosis
- Chronic renal failure
- Pulmonary hypertension

Late onset (>12 months)
- Failure to thrive / weight loss / feeding problems
- Developmental / cognitive impairment
- Seizures
- Muscular hypotonia / muscle weakness
- Thromboembolism / stroke / pulmonary embolism
- Psychiatric disease
- Movement disorder
- Myelopathy
- Atypical haemolytic uraemic syndrome
- Acute metabolic decompensation
- Chronic renal failure
- Cardiac disease

(b) CBS deficiency (classical homocystinuria)*

- Ectopia lentis and/or severe myopia
- Developmental delay/intellectual disability
- Thromboembolic events
- Excessive height and length of the limbs (‘marfanoid’ habitus)
- Osteoporosis and bone deformities (pectus excavatum or carinatum, genu valgum, scoliosis)
- Seizures, psychiatric and behavioural problems and extrapyramidal signs

Work-up of the Patient with Hyperhomocysteinaemia

Generally, tHcy concentrations increase with age: they are lowest in young children and in adults, in pre-menopausal women. If elevated tHcy levels are reported by the laboratory, primarily, common disorders and problems causing secondary, often milder elevation of tHcy such as insufficient supply of Vitamin B12, folate – or (rarely) vitamin B6 – renal insufficiency or hypothyroidism need to be excluded. In CBS deficiency, and the re-methylation disorders, tHcy mostly exceeds 70–100 mmol/L (3, 5).

For further work-up of high levels of tHcy, measurement of the following biochemical parameters is helpful and facilitates focused confirmatory studies: folate, Cbl (eventually vitamin B6), holo-transcobalamin (holo-TC), MMA in blood or urine (urinary MMA is sufficient if renal function is normal) and plasma amino acids (including Met and cystathionine). Propionylcarnitine (C3) is elevated and some acylcarnitine ratios are perturbed in the presence of MMA; thus, the acylcarnitine pattern may be used (and is often used by newborn screening [NBS] programmes) as a preliminary screening parameter if MMA measurement would not immediately be available. Following careful evaluation of biochemical findings, nowadays, molecular genetic studies are the method of choice to confirm an inborn error of metabolism associated with high tHcy. Enzymatic studies, however, still have their place if genetic studies are unavailable or yield inconclusive results (17) (Figure 3).

Some other very rare inborn diseases that may also affect tHcy must be kept in mind as differential diagnoses. tHcy may be, but is not consistently, elevated in haptocorrin deficiency, transcobalamin receptor deficiency (6–8), deficiency of a trifunctional enzyme (5,10-methylenetetrahydrofolate dehydrogenase, 5,10-methenyltetrahydrofolate cyclohydrolase, 10-formyltetrahydrofolate synthetase) in MTHFD1 deficiency (18), as well as in defects of the transcriptional co-regulator HCF1 (19) or THAP11, a thanatos-associated protein (THAP) domain-containing transcription factor (20). In the hypermethioninaemias caused by deficiencies of MAT I/III, glycine N-methyltransferase (GNMT), AdoHcy hydrolase (SAHH) or adenosine kinase (ADK), tHcy is usually normal or only mildly elevated (usually <50 mmol/L) (21, 22).

Isolated defects of MMA metabolism related to mutase dysfunction, as well as the cblD-MMA, cblA and cblB defects, display normal tHcy concentrations (6).

Treatments and Contraindications

Treatment, especially if initiated early, is highly successful in CBS deficiency. Some mutations allow for biochemical (reduction of tHcy) and clinical responsiveness to treatment with the cofactor vitamin B6 (‘B6-responsive’ CBS). B6-responsive patients generally have a milder disease course. At diagnosis of CBS deficiency, a standardised B6 test, as suggested by Morris et al. (4), should be undertaken in every
Martina Huemer. When to measure plasma homocysteine and how to place it in context: the homocystinurias

In the Cbl-related re-methylation disorders, parenteral hydroxo-Cbl (OH-Cbl) is the mainstay of treatment. In the cblC defect, the most frequent of these disorders with several hundreds of patients, it has been clinically observed that cyano-Cbl, an easily available orally applicable Cbl preparation, is ineffective (28). This observation has been explained several years later when it could be shown that the MMACHC gene product decyanates Cbl (29).

Since other Cbl-dependent re-methylation disorders are clinically undistinguishable from the cblC disease, OH-Cbl has consequentially also been the drug of choice in these disorders, and experience with other Cbl preparations is missing. Carnitine, given to remove MMA from the system in combined disorders with both homocystinuria and MMA elevation, and folic or folinic acid, used to prevent deficiencies and optimise the folate cycle, are often applied but have no proven positive effect (5, 17).

In all disorders of re-methylation, nitrous oxide must not be given as it arrests the re-methylation pathway and leads to lethal complications in patients (17, 30, 31). In contrast to CBS deficiency, patients with re-methylation disorders should not be treated with protein-restrictive diet as low protein intake aggravates shortage of both Met and methyl groups and may aggravate the clinical status (5, 17, 32).

patient in whom a B6-unresponsive form is not completely evident, e.g. by family studies.

B6-unresponsive patients, as patients with only partial responsiveness, rely on dietary treatment with restriction of natural protein intake to minimise Met load to consecutively reduce tHcy. Betaine is available as a registered drug for the homocystinurias. It lowers tHcy by opening an alternative re-methylation pathway of Hcy to Met via the enzyme betaine homocysteine methyl transferase. Met must be carefully monitored, because with very high Met levels, single cases of brain oedema have been reported, which responded favourably to betaine withdrawal and consequent lowering of Met. Thus, it is recommended to avoid plasma Met concentrations exceeding 800 (21) or 1000 mmol/L (4). Currently, enzyme replacement therapy for CBS is under development, and it will be interesting to follow up on both the options that this new treatment may open and its limitations (23).

For patients with MTHFR deficiency, betaine is the drug of choice; early treatment with betaine even prevents clinical symptoms (24), and thus NBS should definitely be considered in populations with relevant incidence of the disease (25, 26). In MTHFR deficiency, shortage of 5-MTHF in the brain has been observed, and although this deficiency is of unclear significance, folic acid should not be given since it may aggravate the shortage of 5-MTHF in the brain due to competitive transport at the blood–brain barrier. Significant clinical effects of the often-used supplementation with folinic acid are yet to be proven (27).

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Conclusions

The homocystinurias are treatable disorders, which clinically generally involve the central nervous and multiple other organ systems. The homocystinurias often become clinically evident early in life but may also do so any time later in life. Early treatment may prevent or at least alleviate the burden of the disease. Clinical consideration of these disorders, tHcy measurement and consecutive work-up and allocation of the patient to a specific defect makes a significant difference for affected patients and their families.

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References

1. Fowler B. Homocysteine: overview of biochemistry, molecular biology, and role in disease processes. Semin Vasc Med. 2005;5(2):77–86. doi: 10.1055/s-2005-872394
2. Froese DS, Fowler B, Baumgartner MR. Vitamin B12, folate, and the methionine remethylation cycle-biochemistry, pathways, and regulation. J Inherit Metab Dis. 2019;42(4):673–85. doi: 10.1002/jimd.12009
3. Yap S, Naughten E. Homocystinuria due to cystathionine beta-synthase deficiency in Ireland: 25 years’ experience of a newborn screened and treated population with reference to clinical outcome and biochemical control. J Inherit Metab Dis. 1998;21(7):738–47. doi: 10.1023/a:1005445132327
4. Morris AA, Kožich V, Santra S, Andria G, Ben-Omran TI, Chakravati AB, et al. Guidelines for the diagnosis and management of cystathionine beta-synthase deficiency. J Inherit Metab Dis. 2017;40(1):49–74. doi: 10.1007/s10545-016-9979-0

5. Huemer M, Diodato D, Martinelli D, Olivieri G, Blom H, Gleich F, et al. Phenotype, treatment and outcome in the cobalamin-related remethylation disorders and MTHFR deficiency: Data from the E-HOD registry. J Inherit Metab Dis. 2019;42(2):333–52. doi: 10.1002/jimd.12041

6. Huemer M, Baumgartner MR. The clinical presentation of cobalamin-related disorders: From acquired deficiencies to inborn errors of absorption and intracellular pathways. J Inherit Metab Dis. 2019;42(4):686–705. doi: 10.1002/jimd.20120

7. Stabler SP. Clinical practice. Vitamin B12 deficiency. N Engl J Med. 2013;368(2):149–60. doi: 10.1056/NEJMcp1113996

8. Watkins D, Rosenblatt DS. Inborn errors of cobalamin absorption and metabolism. Am J Med Genet C Semin Med Genet. 2011;157C(1):33–44. doi: 10.1002/ajmg.c.30288

9. Martinelli D, Deodato D, Dionisi-Vici C. Cobalamin C defect: natural history, pathophysiology, and treatment. J Inherit Metab Dis. 2011;34(1):127–35. doi: 10.1007/s10545-010-9161-z

10. Carrillo-Carrasco N, Chandler RJ, Venditti CP. Combined methylmalonic acidemia and homocystinuria, cblC type. I. Clinical presentations, diagnosis and management. J Inherit Metab Dis. 2012;35(1):91–102. doi: 10.1007/s10545-011-9364-y

11. Rosenblatt DS, Aspler AL, Shevell MI, Fletcher BA, Fenton WA, Seashore MR. Clinical heterogeneity and prognosis in combined methylmalonic aciduria and homocystinuria (cblC). J Inherit Metab Dis. 1997;20(4):528–38. doi: 10.1023/a:1005353503003

12. Acipayam C, Güneş H, Güngör O, İpek S, Sarışık N, Demir NŞ. Cerebral atrophy in 21 hypotonic patients with severe vitamin B12 deficiency. J Paediatr Child Health. 2020;56(6):751–6. doi: 10.1111/jpc.14733

13. Roschitz B, Plecko B, Huemer M, Biebl A, Foerster H, Sperl W. Nutritional infantile vitamin B12 deficiency: pathobiological considerations in seven patients. Arch Dis Child Fetal Neonatal Ed. 2005;90(3):F281–2. doi: 10.1136/adc.2004.061929

14. Fischer S, Huemer M, Baumgartner M, Deodato F, Ballhausen D, Boneh A, et al. Clinical presentation and outcome in a series of 88 patients with the cblC defect. J Inherit Metab Dis. 2014;37(5):831–40. doi: 10.1007/s10545-014-9687-6

15. Mudd SH, Skovby F, Levy HL, Pettigrew KD, Wilcken B, Pyeritz RE, et al. The natural history of homocystinuria due to cystathionine beta-synthase deficiency. Am J Hum Genet. 1985;37(1):1–31.

16. Al-Dewik N, Ali A, Mahmoud Y, Shahbeek N, Ali R, Mahmoud L, et al. Natural history, with clinical, biochemical, and molecular characterization of classical homocystinuria in the Qatari population. J Inherit Metab Dis. 2019;42(5):818–30. doi: 10.1002/jimd.12099

17. Huemer M, Diodato D, Schwahn B, Schiff M, Bandeira A, Benoist JF, et al. Guidelines for diagnosis and management of the cobalamin-related remethylation disorders cblC, cblD, cblE, cblF, cblG, cblU and MTHFR deficiency. J Inherit Metab Dis. 2017;40(1):21–48. doi: 10.1007/s10545-016-9991-4

18. Burda P, Kuster A, Hjalmarson O, Suormala T, Bürer C, Lutz SR, et al. Characterization and review of MTHFD1 deficiency: four new patients, cellular delineation and response to folic and folinic acid treatment. J Inherit Metab Dis. 2015;38(5):863–72. doi: 10.1007/s10545-015-9810-3

19. Yu HC, Sloan JL, Scharer G, Brebner A, Quintana AM, Achilly NP, et al. An X-linked cobalamin disorder caused by mutations in transcriptional coregulator HCFC1. Am J Hum Genet. 2013;93(3):506–14. doi: 10.1016/j.ajhg.2013.07.022

20. Quintana AM, Yu HC, Brebner A, Pupavac M, Geiger EA, Watson A, et al. Mutations in THAP11 cause an inborn error of cobalamin metabolism and developmental abnormalities. Hum Mol Genet. 2017;26(15):2838–49. doi: 10.1093/hmg/ddx157

21. Chien YH, Abdenur JE, Baronio F, Bannick AA, Corrales F, Couce M, et al. Mudd’s disease (MAT IIId deficiency): a survey of data for MAT1A homoygotes and compound heteroygotes. Orphanet J Rare Dis. 2015;10:99. doi: 10.1186/s13023-015-0321-y

22. Barić I, Stauffer C, Augoustides-Savvopoulou P, Chien YH, Dobbelare D, Grünert SC, et al. Consensus recommendations for the diagnosis, treatment and follow-up of inherited methyltion disorders. J Inherit Metab Dis. 2017;40(1):5–20. doi: 10.1007/s10545-016-9972-7

23. Bubil EM, Majtan T. Classical homocystinuria: from cystathionine beta-synthase deficiency to novel enzyme therapies. Biochimie. 2020;173:48–56. doi: 10.1016/j.biochi.2019.12.007

24. Diekman EF, de Koning TJ, Verhoeven-Duif NM, Rovers MM, van Hasselt PM. Survival and psychomotor development with early betaine treatment in patients with severe methylenetetrahydrofolate reductase deficiency. JAMA Neurol. 2014;71(2):188–94. doi: 10.1001/jamaneurol.2013.4915

25. Keller R, Chrustina P, Pavlíková M, Gouvéia S, Ribas A, Köller S, et al.; individual contributors of the European Network and Registry for Homocystinurias and Methylation Defects (E-HOD), Barić I, Ben-Omran T, Blasco-Alonso J, Bueno Delgado MA, Carducci C, Cassanelli M, et al. Newborn screening for homocystinurias: Recent recommendations versus current practice. J Inherit Metab Dis. 2019;42(1):128–39. doi: 10.1002/jimd.12034

26. Huemer M, Kožich V, Rinaldo P, Baumgartner MR, Merinero B, Pasquini E, et al. Newborn screening for homocystinurias and methylation disorders: systematic review and proposed guidelines. J Inherit Metab Dis. 2015;38(6):1007–19. doi: 10.1007/s10545-015-9830-z

27. Schiff M, Blom HJ. Treatment of inherited homocystinurias. Neuropediatrics. 2012;43(6):295–304. doi: 10.1055/s-0032-1329883

28. Andersson HC, Shapiro E. Biochemical and clinical response to hydroxocobalamin versus cyanocobalamin treatment in patients with methylenalonic acidemia and homocystinuria (cblC). J Pediatr. 1998;132(1):121–4. doi: 10.1016/s0022-3476(98)70496-2

29. Froese DS, Kopec J, Fitzpatrick F, Schuller M, McCorvie TJ, Chalk R, et al. Structural Insights into the MMACHC-MMADHC
30. Erbe RW, Salis RJ. Severe methylenetetrahydrofolate reductase deficiency, methionine synthase, and nitrous oxide – a cautionary tale. N Engl J Med. 2003;349(1):45–50. doi: 10.1056/NEJMoa021867

31. Selzer RR, Rosenblatt DS, Laxova R, Hogan K. Adverse effect of nitrous oxide in a child with 5,10-methylenetetrahydrofolate reductase deficiency. N Engl J Med. 2003;349(1):45–50. doi: 10.1056/NEJMoa021867

32. Manoli I, Myles JG, Sloan JL, Carrillo-Carrasco N, Morava E, Strauss KA, et al. A critical reappraisal of dietary practices in methylmalonic acidemia raises concerns about the safety of medical foods. Part 2: cobalamin C deficiency. Genet Med. 2016;18(4):396–404. doi: 10.1038/gim.2015.107

33. Weisfeld-Adams JD, Bender HA, Miley-Åkerstedt A, Frempong T, Schrager NL, Patel K, et al. Neurologic and neurodevelopmental phenotypes in young children with early-treated combined methylmalonic acidemia and homocystinuria, cobalamin C type. Mol Genet Metab. 2013;110(3):241–7. doi: 10.1016/j.ymgme.2013.07.018

34. Matos IV, Castejón E, Meavilla S, O’Callaghan M, García-Villoria J, López-Sala A, et al. Clinical and biochemical outcome after hydroxocobalamin dose escalation in a series of patients with cobalamin C deficiency. Mol Genet Metab. 2013;109(4):360–5. doi: 10.1016/j.ymgme.2013.05.007

35. Trefz FK, Scheible D, Frauendienst-Egger G, Huemer M, Suomalainen T, Fowler B, et al. Successful intrauterine treatment of a patient with cobalamin C defect. Mol Genet Metab Rep. 2016;6:55–9. doi: 10.1016/j.ymgmr.2016.01.005