Homocystinuria and Cobalamin Disorders

14

Janet A. Thomas

Contents

J. A. Thomas (✉)
Department of Pediatrics, Section of Clinical Genetics and Metabolism, University of Colorado School of Medicine, Aurora, CO, USA
e-mail: janet.thomas@childrenscolorado.org

L. E. Bernstein et al. (eds.), *Nutrition Management of Inherited Metabolic Diseases*,
https://doi.org/10.1007/978-3-030-94510-7_14

Core Messages

- Homocystinuria is caused by a deficiency in the enzyme, cystathionine-β-synthase (CBS) and results in the accumulation of homocysteine and methionine.
- Homocystinuria is a multisystem disorder with significant morbidity and mortality if untreated.
- The goal of therapy is the reduction of total homocysteine levels.
- Treatment is multifaceted with dietary restriction of methionine and supplementation with betaine, B_6, B_{12}, and folate.
- Outcome is improved with early diagnosis via newborn screening and treatment.
- Disorders of cobalamin metabolism should be considered in patients presenting with hyperhomocysteinemia.

14.1 Homocystinuria Background

Homocystinuria (OMIM# 236200) was first reported in 1962 by Carson, Neill, and colleagues [1]. Two years later, the enzymatic defect was identified [2]. Homocystinuria occurs worldwide, but with variable penetrance depending on ethnicity and methods of ascertainment. The true incidence of homocystinuria is unknown and varies from1 in 1800 (Qatar) to 1 in a million with an overall incidence estimated to be approximately 1 in 200,000 to 300,000 [3–5].

Homocystinuria is an autosomal recessive condition caused by a deficiency of the enzyme, cystathionine-β-synthase (CBS), which results in the accumulation of homocysteine and methionine and a deficiency of cystathionine and cysteine. There are other disorders to consider when an elevated homocysteine concentration is identified.

These disorders include vitamin B_{12} uptake or activation defects, which may or may not have associated elevated methylmalonic acid, severe 5,10-methylenetetrahydrofolate reductase deficiency, and 5-methyl-THF-homocysteine-methyl transferase deficiency. The latter two are typically associated with an elevated homocysteine, but low methionine concentrations, so it is relatively easy to discriminate these conditions from homocystinuria. It is also important to consider that non-genetic causes of hyperhomocysteinemia exist, such as dietary deficiencies, especially folate and vitamin B_{12} deficiency, end-stage renal disease, and administration of several drugs [3, 6]. Pyridoxine (vitamin B_6) is a cofactor for the enzyme, cystathionine-β-synthase. Hence, two forms of homocystinuria are characteristically described: one form in which individuals are responsive to treatment with vitamin B_6 (B_6 responsive homocystinuria) and another form in which individuals are not (B_6 non-responsive homocystinuria). Pyridoxine-responsive patients always have some residual enzyme activity [4].

Homocystinuria may be diagnosed via newborn screening with the detection of elevated methionine on dried blood spots. Although tandem mass spectrometry (MS/MS) is more sensitive for identifying elevated methionine concentrations than past methods, it is estimated that 20–50% of B_6 non-responsive patients may be missed by newborn screening; the majority of B_6–responsive patients are likely missed as well [4, 6, 7]. Consequently, patients diagnosed via newborn screening are seldom B_6-responsive. Specificity of screening is increased by analyzing total homocysteine as a secondary marker and calculating the methionine:total homocysteine ratio [6, 7].

14.2 Biochemistry

Homocysteine is an intermediate metabolite generated during the metabolism of methionine, an essential sulfur-containing amino acid. The biochemical pathways involved in homocystinuria perform two important processes: transsulfuration and remethylation (Fig. 14.1).

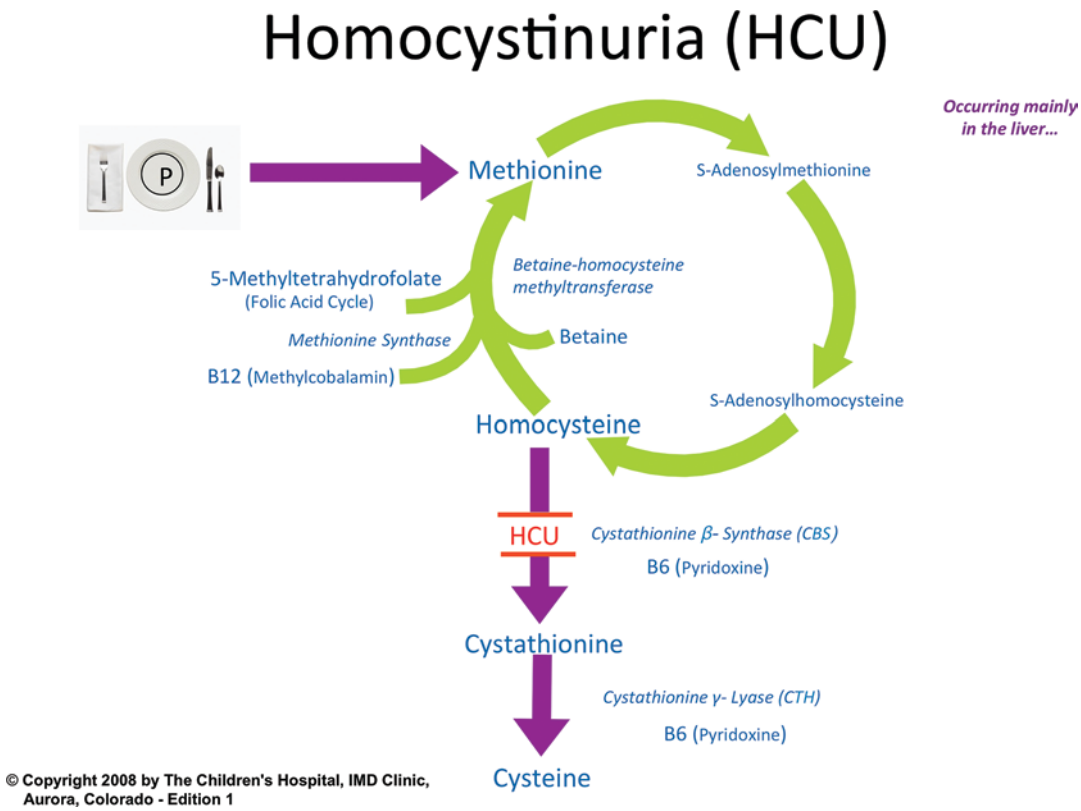


Fig. 14.1 Trans-sulfuration and remethylation in the biochemical pathway of homocystinuria

Trans-sulfuration is facilitated by the action of two vitamin B_6 dependent enzymes, cystathionine-β-synthase (CBS), the enzyme deficient in homocystinuria, and cystathionine-γ-lyase (CTH). CBS catalyzes the condensation of homocysteine and serine to cystathionine and CTH subsequently catalyzes the hydrolysis of cystathionine to cysteine and α-ketobutyrate. Cysteine is important in protein synthesis, taurine synthesis, and is a precursor to glutathione, a strong antioxidant and essential compound in detoxification of many xenobiotics [5, 8, 9].

The remethylation cycle allows the conversion of homocysteine back to methionine by two pathways. The first and major pathway is catalyzed by the enzyme, methionine synthase, and links the folate cycle with homocysteine metabolism. Methionine synthase requires the cofactor, methylcobalamin. The second pathway utilizes the enzyme, betaine-homocysteine methyltransferase [5]. This pathway remethylates homocysteine using a methyl group derived from betaine, formed via oxidation of choline, and is estimated to be responsible for up to 50% of homocysteine remethylation [8]. Both methionine and homocysteine play important roles in protein synthesis, folding, and function.

14.3 Clinical Presentation

Box 14.1: Organ Systems Involved in Homocystinuria

- **Eye**
  Ectopia lentis (lens displacement), myopia, glaucoma, retinal detachment, optic atrophy, cataracts
- **Skeleton**
  Osteoporosis, scoliosis, fractures, tall stature and long extremities, genu valgum, pes cavus, pectus, restricted joint mobility
- **CNS**
  Intellectual disability, seizures, psychiatric disease
- **Vascular**
  Thromboembolic disease, thrombophlebitis, pulmonary embolism, ischemic heart disease

Homocystinuria involves four major organ or body systems (Box 14.1).

14.3.1 Eyes

Ectopia lentis (lens displacement) is often the first sign recognized in an undiagnosed patient and is usually present between 5 and 10 years of age [3, 4]. It may present with severe or rapidly progressive myopia or iridodonesis (quivering of the iris) [6]. Classically, the lens dislocates downwards, in contrast to Marfan syndrome, a condition often considered in the differential diagnosis of homocystinuria, where the lens classically dislocates upwards. Exceptions occur. Lens dislocation may lead to retinal detachment, strabismus, and glaucoma [6]. Other eye findings may include optic atrophy, cataracts, and keratoconus [10].

14.3.2 Skeletal

The skeletal system is also characteristically involved and the features are quite prominent. Individuals with homocystinuria are frequently, but not always, of tall stature with long extremities and long appearing fingers and toes. They are frequently described as having a Marfanoid habitus and hence, homocystinuria should be considered in any individual being evaluated for tall stature and/or Marfan syndrome (NBS Chapter case). Low bone mineral density is a common finding in patients with homocystinuria [11]. Osteoporosis is almost invariably detected after childhood with a tendency to fracture and may lead to vertebral collapse. Other skeletal features include scoliosis, genu valgum (knocked-kneed), pes cavus (high instep), pectus carinatum or excavatum, and restricted joint mobility [4]. Notably, there is a significant connective tissue component in the clinical features of individuals with homocystinuria.

14.3.3 Central Nervous System

Developmental delay affects about 60% of patients to a variable degree [3]. Seizures, EEG abnormalities, and psychiatric disease are also reported. Psychiatric symptoms, such as schizophrenia, depression, and personality disorder, were observed in more than half in one series of 63 patients [12]. In a more recent study, psychological symptoms, especially anxiety and depression, were noted in 64% of the patients (16 of 25 patients) and correlated with lower IQ scores (<85) [13]. There was no correlation with age of diagnosis (NBS and < 2 years of age vs > 2 years of age) or medical complications [13]. Focal neurologic signs may be seen as a consequence of a thromboembolic event [3]. In addition, reversible cerebral white matter lesions, basal ganglia signal abnormalities, and evidence of increased intracranial pressure, as seen on magnetic resonance imaging (MRI), and associated with poor biochemical control has been reported [14, 15].

14.3.4 Vascular System

The largest cause of morbidity and mortality comes from the involvement of the vascular system, particularly from thromboembolic events which can occur in both arteries and veins –

although venous thrombosis is more common than arterial – and in all sizes of vessels [3]. Thrombophlebitis and pulmonary embolism are the most frequent vascular accidents whereas thrombosis of large and medium arteries, especially carotid and renal arteries, are frequent causes of death [4]. Cerebral venous thrombosis may be the presenting feature in both children and adults [6, 16]. Ischemic heart disease is less common. Neuroimaging may demonstrate evidence of infarction or thrombosis. Association with other genotypes linked to increased risk of vascular diseases, such as factor V Leiden and thermolabile methylenetetrahydrofolate reductase, may increase the risk of thrombosis in individuals with homocystinuria [17, 18].

14.3.5 Other

Spontaneous pneumothorax, pancreatitis, lower gastrointestinal bleed, and spontaneous perforation of the small bowel are rare findings reported in homocystinuria [19–21]. In addition, acute liver failure with neurologic involvement has also been reported [22, 23]. A subset of patients may have isolated aortic root dilation similar to that observed in Marfan syndrome [24].

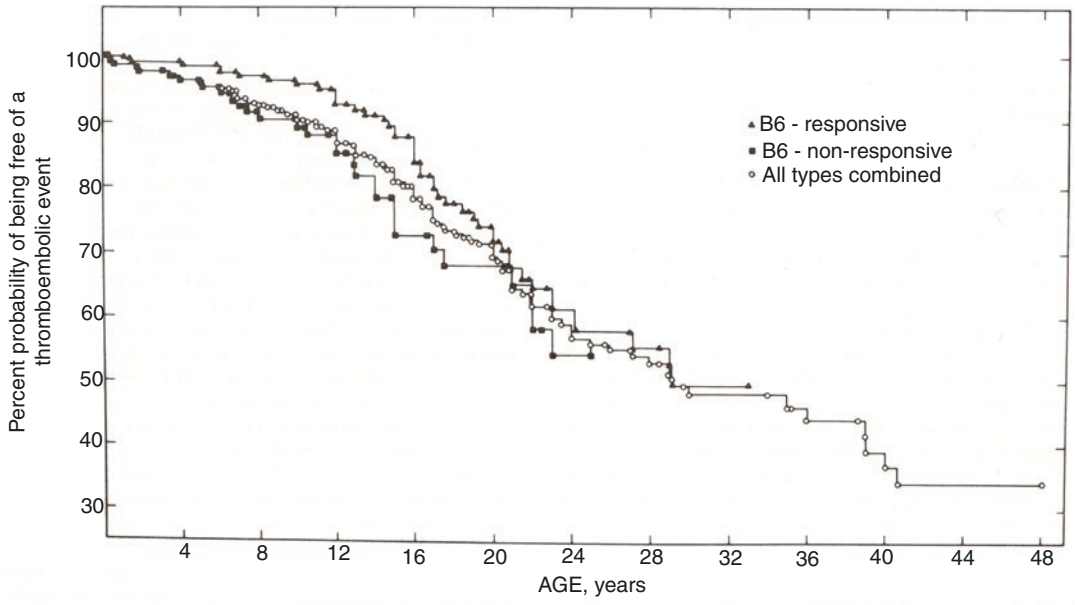
14.4 Natural History

At birth, individuals with homocystinuria appear normal, typically without symptoms in the newborn period or early childhood. This feature makes homocystinuria an excellent candidate condition for newborn screening. Undiagnosed, the condition is progressive with involvement of eyes, skeleton, central nervous system, and vascular system over time. The spectrum of clinical abnormalities is broad as is the age of onset and rate of symptom progression. Treated, however, risks of the complications can be reduced significantly, likely directly related to the reduction in total homocysteine. Good compliance with therapy recommendations may prevent eye disease, osteoporosis, and thromboembolic events and can lead to normal intellectual outcomes [6]. Individuals with B_6 responsive disease generally have milder disease.

Time-to-event curves, based on detailed information on 629 patients, were calculated by Mudd et al. for the main clinical manifestations of homocystinuria [25]. The data demonstrated that the risk for a vascular event was 25% by age 16 years and 50% by age 30 years for both B_6 responsive and B_6 unresponsive forms of homocystinuria (Fig. 14.2). Of the patients in whom events occurred, 51% had peripheral vein thrombosis (with 25% having pulmonary embolism), 32% had cerebral vascular accidents, 11% had peripheral arterial occlusion, 4% had myocardial infarction, and 2% had other ischemic events [25].

The data by Mudd et al. also demonstrated that ectopia lentis occurred by age 6 years in 50% of patients with B_6 unresponsive homocystinuria and by age 10 years in B_6 responsive disease [25]. Eighty-six percent of patients with homocystinuria were ascertained on the basis of ectopia lentis. Finally, the time to event curves demonstrated a > 50% occurrence of radiographic spinal osteoporosis by approximately age 16 years.

It is notable that the aforementioned natural history study that resulted in the data from which the time to event graphs were calculated was published in 1985 and advances in therapy as well as newborn screening have subsequently occurred. Hence, it is likely that the natural history of homocystinuria has changed. New reports suggest that many individuals with homocystinuria may be asymptomatic or may present only with vascular disease later in life [26–28]. Population studies using known common mutations increase the estimate of disease frequency. There are, however, fewer known patients with homocystinuria than would be suggested by known gene mutation rates [26, 27]. This suggests that many patients may be asymptomatic. This also suggests that perhaps the older data represents an ascertainment bias for the natural history of homocystinuria.



Time-to-event graph for initial clinically detected thromboembolic event in untreated patients.

Fig. 14.2 Time-to-event for initial thromboembolic event in untreated patients

14.5 Diagnosis

In 2017, Morris et al. published guidelines for the diagnosis and management of CBS deficiency based on a systematic review of the literature and expert opinion [6]. This article warrants a review. The diagnosis of homocystinuria is based on the recognition of the clinical phenotype in conjunction with the identification of an elevated total plasma homocysteine and elevated (or high normal) plasma methionine concentrations (via quantitative plasma amino acid analysis). Low cystine and low normal to low cystathionine are also seen (Box 14.2). In addition, increased urinary excretion of homocystine as well as cysteine-homocysteine disulfide can be identified on urine amino acid analysis. Notably, the diagnosis can be masked in patients with mild disease who are taking pyridoxine or pyridoxine-fortified multivitamins and foods prior to biochemical testing [6]. Confirmation of the diagnosis can be completed via enzyme assay, typically performed on cultured skin fibroblasts, lymphocytes, or liver tissue, or via molecular studies. Each method may miss the diagnosis and hence, a combination of methods may be needed to confirm the diagnosis in some cases [6]. Molecular analysis is the preferred technique for prenatal diagnosis, although enzyme analysis can be performed on cultured amniocytes, but not in chorionic villi [6].

Box 14.2: Biochemical Features of Untreated Homocystinuria

Disorder	Methionine	L-Cystine	Total homocysteine	Cystathionine
Homocystinuria (CBS deficiency)	↑	↓	↑↑↑	↓

14.6 Pathophysiology

The pathophysiology of homocystinuria appears to be highly complex and is incompletely understood. Much of the pathophysiology is likely due to accumulating homocysteine and it is known that outcomes are improved by lowering homocysteine concentrations. It is known that homocysteine-induced abnormalities of platelets, endothelial cells, and coagulation factors contribute to the hypercoagulable state and/or altered stability of the arterial walls seen in this condition and thus, contribute to the risk for thromboembolic events [3, 29]. Homocysteine is also a known risk factor for early atherosclerosis [29, 30]. Oxidative stress has also been strongly implicated in the vascular injury and remodeling in hyperhomocysteinemia [31]. Elevated homocysteine causes endoplasmic reticulum stress with endothelial dysfunction, glutathione depletion, hydrogen peroxide production, and reactive oxygen species formation with consequent oxidative damage and decreased oxidative antioxidant defenses resulting in protein, lipid, and DNA damage [6, 31–36]. Elevated homocysteine also enhances smooth muscle proliferation and alters intracellular signaling including effects on calcium-activated potassium channel signaling [6, 31].

There is increasing evidence suggesting a role of hydrogen sulfide (H_2S) deficiency in homocystinuria and other cardiovascular diseases [6, 31]. CBS and cystathionine-γ-lyase are key enzymes producing H_2S from homocysteine and/or cysteine [31]. Homocysteine and H_2S have intertwined regulation and patients with homocystinuria demonstrate H_2S deficiency [31]. H_2S is a gasotransmitter molecule also known to regulate bone formation [37]. Experiments in mice models of homocystinuria have demonstrated that normalizing H_2S levels via supplementation can prevent bone loss and improve muscle fatigability seen in the affected mice [37, 38]. Evidence suggests that H_2S inhibits homocysteine-induced oxidative and endoplasmic reticulum stress, mediates endothelial protection, ameliorates homocysteine-induced neurovascular remodeling, and may also function as an antioxidant [31, 38].

In addition, decreased cystathionine and cysteine may also play a role in the pathophysiology of homocystinuria as they are also associated with apoptosis, oxidative stress, and alterations in structural proteins, such as fibrillin and collagen, which may contribute to the connective tissue features of the disorder [6]. A reduction in available cysteine results in weakened collagen and weak collagen likely contributes to the clinical features of lens subluxation, osteoporosis, and skeletal features such as pectus excavatum and marfanoid appearance [39]. Homocysteine is also known to disrupt collagen cross-linking [6]. In addition, disruption of disulfide bonds by the formation of homocysteine-cystine mixed disulfides in fibrillin, a protein important in the lens of the eye, may contribute to the feature of ectopic lentis [40]. Formation of mixed disulfides also contributes to reactive oxygen species formation [36]. Other elements may also play a role in the pathophysiology of homocystinuria. For example, Keating et al. demonstrated evidence of chronic inflammation suggesting that aberrant cytokine expression may be contributing to the pathogenesis of the disease [41] and there is continued controversy as to the role played by altered lipid metabolism [42].

Finally, several hypotheses have been proposed to explain the neurological manifestations seen in individuals with homocystinuria. Orendác et al. proposed a decrease in serine concentration, secondary to an increased remethylation rate, as the cause due to serine's role in the synthesis of myelin [23, 43]. Mudd et al. suggested that the altered S-adenosylmethionine to S-adenosylhomocysteine ratio inhibits transmethylation reactions, including myelin synthesis, contributing to the neurologic manifestations [23, 40].

14.7 Management

The goal of the management of homocystinuria is to reduce or normalize plasma homocysteine concentrations. Management is multifaceted and necessarily individualized and is understandable when one considers the biochemical pathway.

Following diagnosis, all patients with homocystinuria require a trial of vitamin B_6. It is estimated that ~50% of patients with homocystinuria are responsive or partially responsive to B_6 [3]. Responsiveness is chiefly determined by the individual's genotype. Doses of B_6 vary greatly, typically beginning at 10 mg/kg/d or 100 mg/d and progressively increasing to 500 mg/d pending response. Morris and colleagues recommend avoiding doses >500 mg/d [6]. Certainly, doses higher than 1000 mg/d should be avoided due to an association with sensory neuropathy [44, 45]. In responsive patients, the dose of B_6 should be kept at the lowest dose able to achieve adequate metabolic control [8] and plasma total homocysteine levels should be as close to normal as possible or < 50 μmol/L. [6] Total homocysteine concentrations and plasma methionine concentrations can be used to monitor response. Response to B_6 is also influenced by folate depletion, thus, folic acid (5–10 mg/d) or folinic acid (1–5 mg/d) should be given [3, 8]. Low doses of B_6 (50–200 mg/d) are often continued even in those patients determined not to be B_6-responsive due to its role as a cofactor for cystathionine-β-synthase [8, 46]. This latter recommendation is not supported in the recent management guidelines [6].

For individuals who are not fully responsive to B_6, a methionine-restricted diet is necessary as described in Chap. 15.

The other mainstay of therapy is the use of betaine (N,N,N-trimethylglycine) [47]. It is often used in conjunction with a methionine-restricted diet and can improve metabolic control even in individuals with optimal diet control [48, 49]. Betaine is a substrate for the enzyme, betaine-homocysteine methyltransferase, and works to remethylate homocysteine to methionine which consequently lowers homocysteine concentrations but raises methionine concentrations and increases cysteine levels. Betaine may also act as a chemical chaperone and correct partial misfolding of the protein [6]. Moderately elevated methionine concentrations do not appear to have physiological consequences; however, concentrations >1000 nmol/mL have been associated with cerebral edema [50, 51]. Hence, high concentrations of methionine >1000 nmol/mL should be avoided [6]. Betaine is given orally, typically at doses of 150–250 mg/kg/d divided two to three times daily or 6–9 gm/d for children >6 years old and adults; doses up to 20 g/d have been used [3, 8, 52]. For children, the typical starting dose is 50 mg/kg twice daily and for adults 3 gm twice daily. Dose and frequency are adjusted according to biochemical response [6]. There may be limited benefit to utilizing doses higher than 150–200 mg/kg/d [6, 52]. Betaine is well tolerated and has a manageable safety profile [52].

The decision of what modality to begin first, diet vs betaine, is often at the discretion of the treating physician. Unfortunately, achievement of normal total homocysteine concentrations, even with a combination of therapies, is very difficult in most patients. The published guidelines by Morris et al. suggest targeting total homocysteine levels to below 100 μmol/L for optimal control and outcome [6]. Prevention of long-term consequences of homocystinuria requires lifelong therapy. A new therapeutic option, utilizing PEGylated, modified cystathionine-β-synthase enzyme replacement therapy, may prove beneficial and is currently in clinical trials [53–55].

Additional management recommendations vary and remain to be proven. Considerations include a daily aspirin, other antiplatelet aggregation medications (dipyridamole), or anticoagulation therapy, all used to reduce hypercoagulability and thromboembolic risks, and vitamin C supplementation (1 g/d) to ameliorate endothelial dysfunction [3, 9]. Estrogen-containing contraceptives should be avoided due to increased risk of thrombosis [6]. Liver transplantation has been reported as treatment for homocystinuria in two individuals [22, 56]. To further reduce thromboembolic risk, it is important to ensure adequate hydration during times of illness or surgery and to avoid immobilization and long periods of sitting or inactivity. Dehydration and infection increase the risk of venous thrombosis, especially in children [6]. These considerations are most important in individuals with elevated homocysteine concentrations. Management should also include a frequent discussion of the signs and

symptoms of potential complications, such as stroke, deep vein thrombosis, and pulmonary embolism, with the patient, family, or care providers.

Further, if surgery is required for an individual with homocystinuria, it is recommended that dextrose-containing intravenous fluids be started preoperatively and continue throughout the procedure to maintain circulating fluid volume and avoid hypoglycemia. Nitrous oxide should be avoided as postoperative cardiac ischemic episodes have been reported after its administration and use may increase the risk of vascular thrombosis and raise homocysteine concentrations [39, 57–59]. Regional anesthetic techniques may be contraindicated: nerve blocks may be complicated by damage to adjacent blood vessels with the potential for vascular thrombosis and spinal or epidural analgesia may lead to vascular stasis [39]. Surgical management may also include elastic stockings, pneumatic leg compression systems, and early mobilization to aid in the prevention of thromboembolism [59, 60]. Low molecular weight heparin is recommended in cases of prolonged immobilization [6].

14.8 Monitoring and Outcome

Monitoring of an individual with homocystinuria includes the responsiveness to therapeutic interventions as well as monitoring for potential complications. Bone mineral density should be monitored via DEXA scans (dual-energy X-ray absorptiometry) every 3–5 years from adolescence onwards and regular ophthalmology evaluations are recommended [6]. Routine neuroimaging or EEG surveillance is not recommended unless clinically indicated [6]. In addition, patients on a methionine-restricted diet should have consistent monitoring of laboratory values (Chap. 15).

The outcome of homocystinuria has improved with current therapeutic regimes and with early diagnosis via newborn screening [61]. The prognosis is directly associated with the occurrence of vascular ischemia since, as noted, the majority of morbidity and mortality is associated with thromboembolic events. Outcome is also determined by B_6 responsiveness with B_6 responsive patients having an improved prognosis [4, 25]. Historically, almost 25% of individuals with homocystinuria died before the age of 30 years, most commonly from thromboembolism. Thrombosis is also a major risk for pregnant women with homocystinuria, especially in the first 6 weeks postpartum [6]. Lowering homocysteine concentrations significantly reduces the risk of vascular events [48, 62]. Therapy with betaine has contributed to the ability to lower homocysteine concentrations and improve prognosis. Early diagnosis and treatment with good biochemical control can reduce the incidence of ocular complications, osteoporosis, seizures, and thromboembolic events and can lead to normal cognitive development [7, 25, 61, 62]. Family and social support is imperative for successful management and optimal outcome.

14.9 Cobalamin Disorders: Background

Cobalamin (Cbl or vitamin B_{12}) is a water-soluble, organometallic vitamin that is synthesized in lower organisms, but not by higher plants and animals. The only source of Cbl in the human diet is animal products [63, 64]. Cbl is only needed for two reactions in man, but its metabolism involves complex absorption and transport systems and multiple intracellular conversions. As methylcobalamin (MeCbl), it is the cofactor for the enzyme methionine synthase, and as adenosylcobalamin (AdoCbl), it is the cofactor for the enzyme methylmalonyl-CoA mutase [63, 64].

Disorders of Cbl metabolism are generally divided into those involved in the absorption and transport of Cbl and disorders of intracellular utilization. The latter group is further divided into disorders with combined deficiencies of both AdoCbl and MeCbl or deficiencies of each individual cofactor alone. Serum Cbl concentrations are usually low in patients with disorders of absorption and transport (transcobalamin II deficiency is the exception) and usually normal in

disorders of intracellular utilization (although may be reduced in cblF) [64]. Elevated total homocysteine in blood and urine is found in patients with disorders of absorption and transport as well as in defects of intracellular metabolism affecting the synthesis of MeCbl. Elevated methylmalonic acid in blood and urine is seen in disorders affecting the synthesis of AdoCbl. Defects in the earlier, shared pathway of intracellular metabolism result in both homocystinuria/emia and methylmalonic aciduria/emia. Thus, defects in intracellular metabolism of Cbl must be considered in all patients presenting with elevated homocysteine and/or methylmalonic acid in blood and urine. The plasma methionine concentration helps differentiate between Cbl disorders and homocystinuria caused by CBS deficiency; methionine is low or normal in Cbl disorders. Diagnosis of Cbl disorders is now most often confirmed by molecular analysis.

14.10 Clinical Presentation

Disorders of Cbl absorption and transport are rare. Impaired intestinal uptake of dietary Cbl is characteristic of hereditary intrinsic factor (IF) deficiency and Imerslund-Gräsbeck syndrome, a defect in the IF-Cbl receptor [64]. Both typically present between 1 and 5 years of age with developmental delay, failure to thrive, feeding difficulties, and megaloblastic anemia [63]. Individuals with Imerslund-Gräsbeck may develop proteinuria and neurologic symptoms [64]. Transcobalamin (TC) deficiency presents within the first months of life with failure to thrive, vomiting, diarrhea, weakness, and megaloblastic anemia or pancytopenia [63, 64]. TC deficiency has been misdiagnosed as leukemia due to the presence of immature white cell precursors in an otherwise hypocellular bone marrow [63, 64]. Neurologic features may develop with delayed treatment. Individuals with transcobalamin receptor deficiency have been identified via newborn screening. The individuals had moderate elevations of serum methylmalonic acid and, in most cases, also of homocysteine, but did not have clinical symptoms of Cbl deficiency [64]. Similarly, haptocorrin deficiency is characterized by low serum Cbl concentrations without consistent clinical features [64]. Treatment of these conditions involves provision of parenteral hydroxocobalamin (OHCbl), typically with good biochemical response, with the addition of folic acid or folinic acid in TC deficiency [64].

Disorders of intracellular Cbl metabolism have been classified based on the biochemical phenotype and previously on complementation analysis, but now primarily on molecular analysis. The disorders are labeled cblA-G, cblJ, and cblX. Two disorders affecting AdoCbl alone have been classified – cblA and cblB – and present biochemically with methylmalonic aciduria/emia without homocystinuria/emia. Most patients present with a metabolic crisis in the first year of life, similar to classic methylmalonic acidemia secondary to methylmalonyl-CoA mutase deficiency, but later presentations occur. These disorders are often at least partially responsive to Cbl supplementation (cblA more so than cblB). Prognosis remains guarded with late renal and neurologic complications occurring. Two disorders affecting MeCbl alone have also been classified – cblE and cblG – and present biochemically with homocystinuria/emia and low methionine levels without methylmalonic aciduria/emia. The two disorders are indistinguishable from each other clinically and commonly present with megaloblastic anemia and neurologic and ophthalmologic symptoms [7, 65]. The age of presentation is quite variable, from infancy to adulthood, with the majority presenting before 3 years of age [7]. Treatment with OHCbl and betaine is recommended; methionine supplementation may also be needed [64].

Combined defects of both MeCbl and AdoCbl include cblC, cblD, cblF, and cblJ with cblC being the most frequent inborn error of Cbl metabolism [64, 66, 67]. Biochemically, accumulation of both methylmalonic acid and homocysteine are seen in both blood and urine. CblF and cblC typically present in the first year of life and many cblC patients are acutely ill in the first months of life [64]. Symptoms may include feeding difficulties, failure to thrive, developmental delay, and bone marrow suppression with ane-

mia, neutropenia, and thrombocytopenia. An acutely ill infant may demonstrate progressive neurologic deterioration with abnormalities of tone, movement disorder, seizures, and coma. The clinical presentation varies considerably, and multisystem involvement occurs with liver, renal, pulmonary, and cardiac involvement [64–67]. Focal segmental glomerulorsclerosis, atypical glomerulopathy, and thrombotic microangiopathy leading to hemolytic uremic syndrome and pulmonary hypertension may also occur [7, 65–67]. In addition, patients with cblC develop a pigmentary retinopathy that is progressive over time despite appropriate therapy. CblC is one of the few disorders that can present with infantile maculopathy typically progressing to a "bull's eye" maculopathy by 6–12 months of age and leading to blindness within the first decade of life [65, 67]. Intrauterine growth retardation, mild facial dysmorphism, congenital malformations, most commonly structural congenital heart disease, and fetal cardiomyopathy may be seen suggesting in utero involvement [63, 64, 67]. Further, late-onset forms of cblC, including adult presentations, are well known [64, 66, 67].

Rare individuals with cblJ have been described with a similar infantile presentation as above or a later onset form (4 and 6 years of age) with hyperpigmentation and prematurely grey hair; macrocytic anemia was present in all cases [64]. The presentation of cblD is variable with the first patients described presenting in adolescence with behavioral difficulties, mild cognitive impairment and neurologic symptoms [68]. Rare additional patients have been described. Individuals with cblD may present with combined deficiency of MeCbl and AdoCbl or with isolated defects – homocystinuria in cblD variant 1 and methylmalonic aciduria in cblD variant 2, the variation determined by genotype [64, 65].

Most recently, cblX has been described [69]. This is the only X-linked disorder of Cbl metabolism known, the others being autosomal recessive. CblX involves pathways outside of those of central Cbl synthesis and intracellular transport. Patients present in the first months of life with a similar presentation to cblC patients, but typically develop more severe neurologic disease [64]. The majority of patients (90%) have intractable epilepsy, usually with severe developmental delay and microcephaly (50%) [70]. Cortical malformations and congenital anomalies may be present [71]. All patients described have had a moderate increase in methylmalonic acid concentrations with several patients also having elevated homocysteine [64].

14.11 Management and Outcome

Guidelines for the diagnosis and management of Cbl disorders have been published [65]. Treatment primarily involves provision of parenteral OHCbl (IV, IM, SC), betaine (250 mg/kg/d) with or without folinic acid (5–30 mg daily) and carnitine (50–100 mg/kg/d); the latter two used without clear beneficial effects [64, 65, 67]. Cyanocobalamin (CNCbl) is not as effective as OHCbl in the treatment of these disorders [64, 67]. The beginning dose of OHCbl is typically 0.3 mg/kg/d and is titrated upwards pending biochemical response. This often requires high doses up to 20 mg daily [63, 66, 67]. Patients with cblA and cblB may respond to a protein-restricted diet; however, such diets are not recommended in cblC, particularly with the use of methionine-restricted formulas [65, 67, 72]. Methionine supplementation may be required to maintain normal serum methionine concentrations [65]. Metabolite levels can be improved with treatment, but clinical improvement is variable, and mortality and morbidity remain high [63, 65, 66, 73].

Early treatment is important and appears to improve survival, corrects hematologic abnormalities, and prevents some of the long-term consequences, but has little effect on the eye disease or the neurocognitive outcome [65, 66]. Newborn screening detecting elevated C3 acylcarnitines from methylmalonic acid has increasingly led to the diagnosis of Cbl defects in the newborn period. The positive predictive value can be substantially increased by performing methylmalonic acid or total homocysteine levels as second-tier analytes [65]. Newborn screening for cblD, cblE, and cblG may be feasible by detecting low methionine and methionine to phenylalanine ratio [65].

Second-tier testing with total homocysteine differentiates patients from controls [65]. Prenatal treatment with administration of OHCbl to the mother has been described [64, 67].

References

1. Carson NA, Neill DW. Metabolic abnormalities detected in a survey of mentally backward individuals in Northern Ireland. Arch Dis Child. 1962;37:505–13.
2. Mudd SH, Finkelstein JD, Irreverre F, Laster L. Homocystinuria: an enzymatic defect. Science. 1964;143(3613):1443–5.
3. Andria G, Fowler B, Sebastio G. Disorders of sulfur amino acid metabolism. In: Saudubray JM, Walter JH, editors. Inborn metabolic diseases: diagnosis and treatment. 5th ed. Berlin: Springer-Verlag; 2012.
4. Nyhan WL, Barshop BA, Ozand PT. Homocystinuria. In: Atlas of metabolic diseases. 2nd ed. London: Hodder Arnold; 2005.
5. Blom HJ, Smulders Y. Overview of homocysteine and folate metabolism. With special references to cardiovascular disease and neural tube defects. J Inherit Metab Dis. 2011;34(1):75–81.
6. Morris AA, Kozich V, Santra S, Andria G, Ben-Omran TI, Chakrapani AB, et al. Guidelines for the diagnosis and management of cystathionine beta-synthase deficiency. J Inherit Metab Dis. 2017;40(1):49–74.
7. Huemer M, Burer C, Jesina P, Kozich V, Landolt MA, Suormala T, et al. Clinical onset and course, response to treatment and outcome in 24 patients with the cblE or cblG remethylation defect complemented by genetic and in vitro enzyme study data. J Inherit Metab Dis. 2015;38(5):957–67.
8. Schiff M, Blom HJ. Treatment of inherited homocystinurias. Neuropediatrics. 2012;43(6):295–304.
9. Pullin CH, Bonham JR, McDowell IF, Lee PJ, Powers HJ, Wilson JF, et al. Vitamin C therapy ameliorates vascular endothelial dysfunction in treated patients with homocystinuria. J Inherit Metab Dis. 2002;25(2):107–18.
10. Gus PI, Pilati NP, Schoenardie BO, Marinho DR. Classic homocystinuria and keratoconus: a case report. Arq Bras Oftalmol. 2018;81(4):336–8.
11. Weber DR, Coughlin C, Brodsky JL, Lindstrom K, Ficicioglu C, Kaplan P, et al. Low bone mineral density is a common finding in patients with homocystinuria. Mol Genet Metab. 2016;117(3):351–4.
12. Abbott MH, Folstein SE, Abbey H, Pyeritz RE. Psychiatric manifestations of homocystinuria due to cystathionine beta-synthase deficiency: prevalence, natural history, and relationship to neurologic impairment and vitamin B6-responsiveness. Am J Med Genet. 1987;26(4):959–69.
13. Almuqbil MA, Waisbren SE, Levy HL, Picker JD. Revising the psychiatric phenotype of homocystinuria. Genet Med. 2019;21(8):1827–31.
14. Sasai H, Shimozawa N, Asano T, Kawamoto N, Yamamoto T, Kimura T, et al. Successive MRI findings of reversible cerebral white matter lesions in a patient with cystathionine beta-synthase deficiency. Tohoku J Exp Med. 2015;237(4):323–7.
15. Li CQ, Barshop BA, Feigenbaum A, Khanna PC. Brain magnetic resonance imaging findings in poorly controlled homocystinuria. J Radiol Case Rep. 2018;12(1):1–8.
16. Woods E, Dawson C, Senthil L, Geberhiwot T. Cerebral venous thrombosis as the first presentation of classical homocystinuria in an adult patient. BMJ Case Rep. 2017;2017
17. Mandel H, Brenner B, Berant M, Rosenberg N, Lanir N, Jakobs C, et al. Coexistence of hereditary homocystinuria and factor V Leiden–effect on thrombosis. N Engl J Med. 1996;334(12):763–8.
18. Kluijtmans LA, Boers GH, Verbruggen B, Trijbels FJ, Novakova IR, Blom HJ. Homozygous cystathionine beta-synthase deficiency, combined with factor V Leiden or thermolabile methylenetetrahydrofolate reductase in the risk of venous thrombosis. Blood. 1998;91(6):2015–8.
19. De Franchis R, Sperandeo MP, Sebastio G, Andria G. Clinical aspects of cystathionine beta-synthase deficiency: how wide is the spectrum? The Italian Collaborative Study Group on Homocystinuria. Eur J Pediatr. 1998;157(Suppl 2):S67–70.
20. Muacevic-Katanec D, Kekez T, Fumic K, Baric I, Merkler M, Jakic-Razumovic J, et al. Spontaneous perforation of the small intestine, a novel manifestation of classical homocystinuria in an adult with new cystathionine beta-synthetase gene mutations. Coll Antropol. 2011;35(1):181–5.
21. Al Humaidan M, Al Sharkawy I, Al Sanae A, Al Refaee F. Homocystinuria with lower gastrointestinal bleeding: first case report. Med Princ Pract. 2013;22(5):500–2.
22. Snyderman SE. Liver failure and neurologic disease in a patient with homocystinuria. Mol Genet Metab. 2006;87(3):210–2.
23. Gupta P, Goyal S, Grant PE, Fawaz R, Lok J, Yager P, et al. Acute liver failure and reversible leukoencephalopathy in a pediatric patient with homocystinuria. J Pediatr Gastroenterol Nutr. 2010;51(5):668–71.
24. Lorenzini M, Guha N, Davison JE, Pitcher A, Pandya B, Kemp H, et al. Isolated aortic root dilation in homocystinuria. J Inherit Metab Dis. 2018;41(1):109–15.
25. 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.
26. Janosik M, Sokolova J, Janosikova B, Krijt J, Klatovska V, Kozich V. Birth prevalence of homocystinuria in Central Europe: frequency and pathogenicity of mutation c.1105C>T (p.R369C) in the cystathionine beta-synthase gene. J Pediatr. 2009;154(3):431–7.

27. Skovby F, Gaustadnes M. A revisit to the natural history of homocystinuria due to cystathionine beta-synthase deficiency. Mol Genet Metab. 2010;99(1):1–3.
28. Magner M, Krupkova L, Honzik T, Zeman J, Hyanek J, Kozich V. Vascular presentation of cystathionine beta-synthase deficiency in adulthood. J Inherit Metab Dis. 2011;34(1):33–7.
29. Moghadasian MH, McManus BM, Frohlich JJ. Homocyst(e)ine and coronary artery disease. Clinical evidence and genetic and metabolic background. Arch Intern Med. 1997;157(20):2299–308.
30. Boushey CJ, Beresford SA, Omenn GS, Motulsky AG. A quantitative assessment of plasma homocysteine as a risk factor for vascular disease. Probable benefits of increasing folic acid intakes. JAMA. 1995;274(13):1049–57.
31. Yang Q, He GW. Imbalance of homocysteine and H2S: significance, mechanisms, and therapeutic promise in vascular injury. Oxidative Med Cell Longev. 2019;2019:7629673.
32. Tsai JC, Perrella MA, Yoshizumi M, Hsieh CM, Haber E, Schlegel R, et al. Promotion of vascular smooth muscle cell growth by homocysteine: a link to atherosclerosis. Proc Natl Acad Sci U S A. 1994;91(14):6369–73.
33. Loscalzo J. The oxidant stress of hyperhomocyst(e)inemia. J Clin Invest. 1996;98(1):5–7.
34. Vanzin CS, Biancini GB, Sitta A, Wayhs CA, Pereira IN, Rockenbach F, et al. Experimental evidence of oxidative stress in plasma of homocystinuric patients: a possible role for homocysteine. Mol Genet Metab. 2011;104(1–2):112–7.
35. Vanzin CS, Manfredini V, Marinho AE, Biancini GB, Ribas GS, Deon M, et al. Homocysteine contribution to DNA damage in cystathionine beta-synthase-deficient patients. Gene. 2014;539(2):270–4.
36. Richard E, Gallego-Villar L, Rivera-Barahona A, Oyarzabal A, Perez B, Rodriguez-Pombo P, et al. Altered redox homeostasis in branched-chain amino acid disorders, organic acidurias, and homocystinuria. Oxidative Med Cell Longev. 2018;2018:1246069.
37. Behera J, Kelly KE, Voor MJ, Metreveli N, Tyagi SC, Tyagi N. Hydrogen sulfide promotes bone homeostasis by balancing inflammatory cytokine signaling in CBS-deficient mice through an epigenetic mechanism. Sci Rep. 2018;8(1):15226.
38. Majumder A, Singh M, Behera J, Theilen NT, George AK, Tyagi N, et al. Hydrogen sulfide alleviates hyperhomocysteinemia-mediated skeletal muscle atrophy via mitigation of oxidative and endoplasmic reticulum stress injury. Am J Physiol Cell Physiol. 2018;315(5):C609–C22.
39. Bissonnette B, Luginbuehl I, Marciniak B. Homocystinuria in syndromes: rapid recognition and perioperative implications. New York: McGraw Hill Companies; 2006.
40. Mudd SH, Levy HL, Kraus JP. Disorders of transsulferation. Metabolic and molecular basis of inherited disease. New York: McGraw Hill Companies; 2001.
41. Keating AK, Freehauf C, Jiang H, Brodsky GL, Stabler SP, Allen RH, et al. Constitutive induction of pro-inflammatory and chemotactic cytokines in cystathionine beta-synthase deficient homocystinuria. Mol Genet Metab. 2011;103(4):330–7.
42. Poloni S, Schweigert Perry ID, D'Almeida V, Schwartz IV. Does phase angle correlate with hyperhomocysteinemia? A study of patients with classical homocystinuria. Clin Nutr. 2013;32(3):479–80.
43. Orendac M, Zeman J, Stabler SP, Allen RH, Kraus JP, Bodamer O, et al. Homocystinuria due to cystathionine beta-synthase deficiency: novel biochemical findings and treatment efficacy. J Inherit Metab Dis. 2003;26(8):761–73.
44. Echaniz-Laguna A, Mourot-Cottet R, Noel E, Chanson JB. Regressive pyridoxine-induced sensory neuronopathy in a patient with homocystinuria. BMJ Case Rep. 2018;2018
45. Bendich A, Cohen M. Vitamin B6 safety issues. Ann N Y Acad Sci. 1990;585:321–30.
46. Baric I, Fowler B. Sulphur amino acids. In: Blau N, et al., editors. Physician's guide to the diagnosis, treatment, and follow-up of inherited metabolic diseases. Heidelberg: Springer-Verlag; 2014. p. 43.
47. Lawson-Yuen A, Levy HL. The use of betaine in the treatment of elevated homocysteine. Mol Genet Metab. 2006;88(3):201–7.
48. Wilcken DE, Wilcken B. The natural history of vascular disease in homocystinuria and the effects of treatment. J Inherit Metab Dis. 1997;20(2):295–300.
49. Singh RH, Kruger WD, Wang L, Pasquali M, Elsas LJ 2nd. Cystathionine beta-synthase deficiency: effects of betaine supplementation after methionine restriction in B6-nonresponsive homocystinuria. Genet Med. 2004;6(2):90–5.
50. Yaghmai R, Kashani AH, Geraghty MT, Okoh J, Pomper M, Tangerman A, et al. Progressive cerebral edema associated with high methionine levels and betaine therapy in a patient with cystathionine beta-synthase (CBS) deficiency. Am J Med Genet. 2002;108(1):57–63.
51. Devlin AM, Hajipour L, Gholkar A, Fernandes H, Ramesh V, Morris AA. Cerebral edema associated with betaine treatment in classical homocystinuria. J Pediatr. 2004;144(4):545–8.
52. Valayannopoulos V, Schiff M, Guffon N, Nadjar Y, Garcia-Cazorla A, Martinez-Pardo Casanova M, et al. Betaine anhydrous in homocystinuria: results from the RoCH registry. Orphanet J Rare Dis. 2019;14(1):66.
53. Bublil EM, Majtan T, Park I, Carrillo RS, Hulkova H, Krijt J, et al. Enzyme replacement with PEGylated cystathionine beta-synthase ameliorates homocystinuria in murine model. J Clin Invest. 2016;126(6):2372–84.
54. Koeberl DD. Vision of correction for classic homocystinuria. J Clin Invest. 2016;126(6):2043–4.
55. Majtan T, Park I, Cox A, Branchford BR, di Paola J, Bublil EM, et al. Behavior, body composition, and vascular phenotype of homocystinuric mice on

methionine-restricted diet or enzyme replacement therapy. FASEB J. 2019;33(11):12477–86.
56. Lin NC, Niu DM, Loong CC, Hsia CY, Tsai HL, Yeh YC, et al. Liver transplantation for a patient with homocystinuria. Pediatr Transplant. 2012;16(7):E311–4.
57. Koblin DD. Homocystinuria and administration of nitrous oxide. J Clin Anesth. 1995;7(2):176.
58. Badner NH, Beattie WS, Freeman D, Spence JD. Nitrous oxide-induced increased homocysteine concentrations are associated with increased postoperative myocardial ischemia in patients undergoing carotid endarterectomy. Anesth Analg. 2000;91(5):1073–9.
59. Asghar A, Ali FM. Anaesthetic management of a young patient with homocystinuria. J Coll Physicians Surg Pak. 2012;22(11):720–2.
60. Lowe S, Johnson DA, Tobias JD. Anesthetic implications of the child with homocystinuria. J Clin Anesth. 1994;6(2):142–4.
61. 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.
62. Yap S, Boers GH, Wilcken B, Wilcken DE, Brenton DP, Lee PJ, et al. Vascular outcome in patients with homocystinuria due to cystathionine beta-synthase deficiency treated chronically: a multicenter observational study. Arterioscler Thromb Vasc Biol. 2001;21(12):2080–5.
63. Watkins D, Rosenblatt DS. Inborn errors of cobalamin absorption and metabolism. Am J Med Genet C Semin Med Genet. 2011;157C(1):33–44.
64. Watkins D, Rosenblatt DS, Fowler B. Disorders of cobalamin and folate transport and metabolism. In: Saudubray JM, Baumgartner M, Walter J, editors. Inborn metabolic diseases: diagnosis and treatment. 6th ed. Berlin: Springer-Verlag; 2016. p. 385–99.
65. 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, cblJ and MTHFR deficiency. J Inherit Metab Dis. 2017;40(1):21–48.
66. Martinelli D, Deodato F, Dionisi-Vici C. Cobalamin C defect: natural history, pathophysiology, and treatment. J Inherit Metab Dis. 2011;34(1):127–35.
67. 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.
68. Goodman SI, Moe PG, Hammond KB, Mudd SH, Uhlendorf BW. Homocystinuria with methylmalonic aciduria: two cases in a sibship. Biochem Med. 1970;4(5):500–15.
69. 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.
70. Scalais E, Osterheld E, Weitzel C, De Meirleir L, Mataigne F, Martens G, et al. X-linked cobalamin disorder (HCFC1) mimicking nonketotic hyperglycinemia with increased both cerebrospinal fluid glycine and methylmalonic acid. Pediatr Neurol. 2017;71:65–9.
71. Gerard M, Morin G, Bourillon A, Colson C, Mathieu S, Rabier D, et al. Multiple congenital anomalies in two boys with mutation in HCFC1 and cobalamin disorder. Eur J Med Genet. 2015;58(3):148–53.
72. 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.
73. Weisfeld-Adams JD, Bender HA, Miley-Akerstedt 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.