Disorders of Sulfur Amino Acid and Hydrogen Sulfide Metabolism

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Summary

The conversion of methionine to inorganic sulfate involves the formation of homocysteine encompassing transmethylation followed by transsulfuration. Several inherited enzyme deficiencies within this pathway have been described. Those causing hypermethioninemia may be confused with the many known secondary causes of increased methionine demanding diagnostic expediency. Most of the disorders have been described in small numbers of patients so that the full clinical spectrum of these is not known. Exceptions are methionine adenosyltransferase (MAT) I/III deficiency and cystathionine ß-synthase deficiency which causes classical homocystinuria, characterized primarily by an increased risk of thrombosis and embolism, lens dislocation, and other connective tissue involvement and cognitive impairment. While methionine adenosyltransferase I/III deficiency is only symptomatic in some patients causing different neurological problems and glycine *N*-methyltransferase deficiency affects liver function, other diseases causing hypermethioninemias may be associated with a multisystem disease of varying severity and progression. MAT II deficiency can be associated with thoracic aortic aneurysms in some heterozygotes for *MAT2* mutations. Methanethiol oxidase deficiency causes cabbage-like breath odor (extraoral halitosis). The association of mercaptopyruvate sulfur transferase deficiency with cognitive impairment, as the only disease characteristic, is questionable. Isolated sulfite oxidase deficiency is characterized by refractory convulsions in early infancy, brain atrophy, severe psychomotor retardation, and lens dislocation. Ethylmalonic encephalopathy is a severe disorder manifesting with seizures, developmental delay and cognitive impairment, orthostatic acrocyanosis and petechia due to vasodilation, failure to thrive, and chronic hemorrhagic diarrhea. Measurement of plasma and urine amino acids and total homocysteine can detect many of the disorders described in this chapter, while other tests are necessary for others. Confirmatory tests are enzyme assays and/or mutation analysis. Treatment combines one or more of dietary restriction of precursors, substitution of essential products, pharmacologic doses of cofactors, and binding and removing of harmful metabolites. Early diagnosis and early treatment favor better outcome.

Introduction

Sulfur-containing amino acids include methionine, homocysteine, cystathionine, cysteine, and taurine. This chapter deals with inherited deficiencies of enzymes in the transmethylation and transsulfuration pathways that convert sulfur from methionine via homocysteine and cysteine to sulfate, including sulfide metabolism (Fig. 22.1). Since adenosine kinase deficiency also disrupts the methionine cycle, it is included in this chapter.

Most disorders described in this chapter are inherited as autosomal recessive traits. Exceptions are autosomal dominant forms of methionine adenosyltransferase (MAT) II deficiency and a subgroup of MAT I/III deficiency, caused by mutations with dominant negative effect on the wild-type allele (Chamberlin et al. 1997).

Pathophysiology of disorders of sulfur-containing amino acids is complex and only partly understood (Kožich et al. 2016). In disorders associated with hypermethioninemia, very high concentrations can be harmful themselves, primarily for the brain. In MAT I/III deficiency, low adenosylmethionine (AdoMet) and subsequent deficient methylation could be contributing factors. There are several hypotheses of how *MAT2A* loss-of-function mutations could lead to aortic disease, and it is possible that they require a second "hit" (Guo et al. 2015). Methionine can be also transaminated yielding methanethiol; deficiency of methanethiol oxidase results in accumulation of malodorous molecules such as methanethiol and dimethylsulfide. In *S*-adenosylhomocysteine (AdoHcy) hydrolase deficiency, high concentrations of AdoHcy inhibit numerous methyltransferases with very variable clinical consequences. Several putative pathogenetic mechanisms of adenosine kinase deficiency are related to increased adenosine and its various toxic effects. Another mechanism could be inhibition of numerous methyltransferases caused by secondary elevation of *S*-adenosylhomocysteine. The latter mechanism could also be important in classical homocystinuria, where a major pathogenetic mechanism seems to be elevation of homocysteine with its adverse effect on coagulation, vessels and secondary to vascular changes in many tissues, and possibly the decreased production of cysteine manifesting in connective tissue including lens zonular fibers. Clinical consequences of sulfite oxidase deficiency are likely due to toxic effects of sulfite, *S*-sulfocysteine, and thiosulfate on the brain and connective tissue. Patients with ethylmalonic encephalopathy accumulate a large amount of hydrogen sulfide, which leads directly to vasodilation and to secondary inhibition of cytochrome c-oxidase with subsequent impairment of short-chain fatty oxidation with typical metabolite changes and of oxidative phosphorylation with lactic acidosis.

Clinical presentation can occur at any age and varies widely in its severity.

MAT I/III deficiency is asymptomatic in all individuals with the autosomal dominant disease, while about half of the patients with the autosomal recessive form have developed neurological symptoms (Chien et al. 2015). Hypermethioninemia, the biochemical hallmark of this

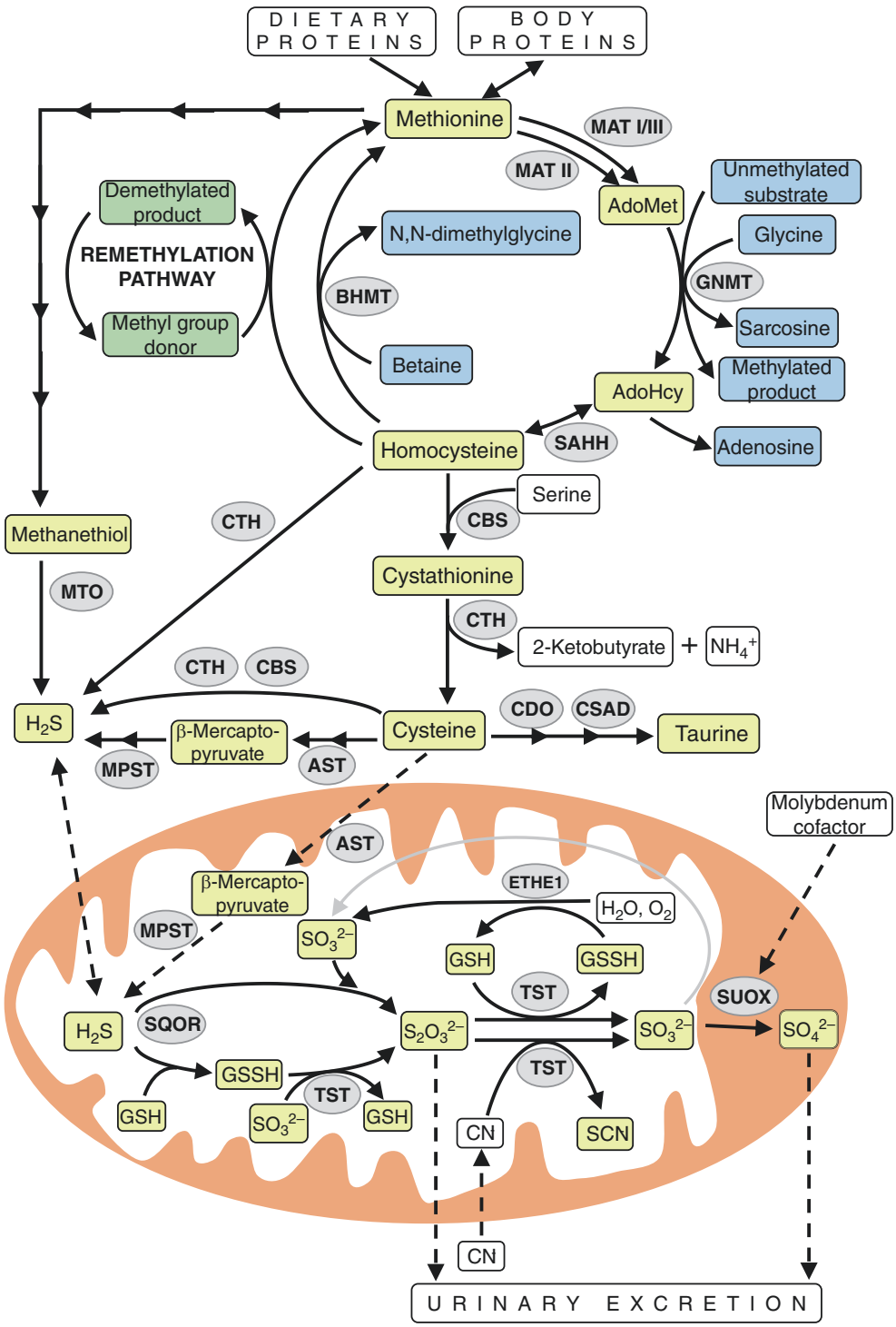

Fig. 22.1 Metabolism of sulfur amino acids and of hydrogen sulfide. Methionine is converted to cysteine via a series of reactions involving the following enzymes: *MATI/III* methionine adenosyltransferase I/III, *MATII* methionine adenosyltransferase II, *GNMT* glycine *N*-methyltransferase, *SAHH* *S*-adenosylhomocysteine hydrolase, *BHMT* betaine homocysteine methyltransferase, *CBS* cystathionine beta-synthase, *CTH* cystathionine gamma-lyase, *AdoMet* *S*-adenosylmethionine, *AdoHcy* *S*-adenosylhomocysteine. Cysteine serves as the major precursor for synthesis of hydrogen sulfide catalyzed by CBS, CTH, aspartate aminotransferase (AST), and mercaptopyruvate sulfurtransferase (MPST); hydrogen sulfide may be also synthesized by methanethiol oxidase (MTO). Another route of cysteine oxidation to taurine is catalyzed by cysteine dioxygenase (CDO) and cysteine sulfinic acid decarboxylase (CSAD). Mitochondrial oxidation of hydrogen sulfide requires the following enzymes: *SQOR* sulfide:quinone oxidoreductase, *ETHE1* persulfide dioxygenase, *TST* thiosulfate transferase, *SUOX* sulfite oxidase, *GSH* glutathione, *GSSH* glutathione persulfide

disease, if severe, is itself associated with increased risk of various neurological problems (Braverman et al. 2005). The most characteristic brain imaging changes are demyelination with edema of subcortical and deep white matter, more pronounced in dorsal brain stem and resulting in separation of myelin layers—the so-called vacuolating myelinopathy (Braverman et al. 2005). Neurological abnormalities tend to occur in patients with plasma methionine concentrations generally above 800 μmol/L, whereas they have been rare in subjects with lower levels (Chien et al. 2015).

MAT II deficiency is only a risk factor for developing thoracic aortic aneurysms in some heterozygotes for *MAT2A* mutations.

Glycine N-methyltransferase (GNMT) deficiency (Mudd et al. 2001) has been so far described in only five children. The only clinical sign was mild hepatomegaly present in two

siblings. The patients have remained clinically well during follow-up (Barić et al. 2017). Their aminotransferase activities ranged from borderline to fivefold increase. Plasma methionine can reach potentially damaging values (see MAT I/III deficiency).

S-adenosylhomocysteine hydrolase deficiency (Barić et al. 2004) has been proven and reported so far in ten patients. Two sibs had fetal hydrops, liver synthetic failure, and muscular hypotonia leading to respiratory failure and death in early infancy. They also showed brain abnormalities including cerebellar and pontine hypoplasia, hypoplastic corpus callosum, and hypomyelination. Muscle disease with high creatine kinase was present also in other patients with a milder phenotype. They also had, in various combinations, developmental delay, behavioral abnormalities, myelination delay, strabismus, coagulopathy, and liver disease. One patient had hepatocellular carcinoma, and there is some evidence that this disease carries increased risk for this malignancy.

Adenosine kinase deficiency has been described so far in 19 patients. All had severe developmental delay, hypotonia, and frontal bossing. The majority had hypertelorism, failure to thrive, epilepsy, macrocephaly, neonatal jaundice, and liver disease with elevated aminotransferases. About half of patients had cardiac anomalies (Staufner et al. 2016; Alhusani et al. 2019).

Cystathionine beta-synthase (CBS) deficiency is clinically variable and characterized primarily by an increased risk of thrombosis—predominantly in venous beds—and pulmonary embolism and in more severe forms by osteoporosis, lenticular myopia and lens dislocation, developmental delay, and cognitive impairment (Mudd et al. 1985). About half of patients are pyridoxine responsive with a less severe disease (Morris et al. 2017).

Cystathionase deficiency is considered a benign condition (Kraus et al. 2009) although it was originally described in patients with psychomotor retardation and other neurological findings.

Methanethiol oxidase (MTO) deficiency has been described in only five patients with cabbage-like breath odor (extraoral halitosis) due to accumulation of methanethiol and dimethylsulfide (Pol et al. 2018).

Isolated sulfite oxidase deficiency is characterized by refractory convulsions starting in the neonatal or early infantile period, severe psychomotor retardation, brain imaging findings resembling hypoxic-ischemic encephalopathy with development of cysts, and early death. Lens dislocation occurs usually after the neonatal period. Milder and late-onset cases have been reported (Claerhout et al. 2018; Bindu et al. 2017, see Online resources).

Persulfide dioxygenase (PDO) deficiency or ethylmalonic encephalopathy (ETHE1) is a severe disorder manifesting in seizures, developmental delay and cognitive impairment, orthostatic acrocyanosis and petechia due to vasodilation, failure to thrive, and chronic hemorrhagic diarrhea (Di Meo et al. 2017, see Online resources).

Mercaptopyruvate sulfur transferase (MPST) deficiency and/or excretion of the mercaptolactate has been reported in two patients with mental retardation (Ampola et al. 1969); however, subsequently no association with cognitive impairment was reported.

Nomenclature

No.	Disorder	Alternative name	Abbreviation of the disease/ deficiency	Gene symbol	Chromosomal localization	Mode of inheritance	Affected protein	OMIM No.	Subtype
22.1	Methionine adenosyltransferase I/III deficiency	MAT deficiency	MAT I/III	*MAT1A*	10q22	AR	Methionine adenosyltransferase I/III	250850	Potentially symptomatic form
22.1	Methionine adenosyltransferase I/III deficiency	MAT deficiency	MAT I/III	*MAT1A*	10q22	AD	Methionine adenosyltransferase I/III	250850	Benign form
22.2	Methionine adenosyltransferase II deficiency	*S*-adenosylmethionine synthase isoform type 2 deficiency; MATII deficiency	MATII	*MAT2A*	2p11.2	AD	Methionine adenosyltransferase II alpha	601468	Potentially symptomatic
22.3	Glycine *N*-methyltransferase deficiency	GNMT deficiency	GNMT	*GNMT*	6p12	AR	Glycine *N*-methyltransferase	606664	All forms
22.4	*S*-adenosylhomocysteine hydrolase deficiency	SAHH deficiency	AHCY	*AHCY*	20q11.22	AR	Adenosylhomocysteinase, *S*-adenosylhomocysteine hydrolase	613752	All forms

No.	Disorder	Alternative name	Abbreviation of the disease/ deficiency	Gene symbol	Chromosomal localization	Mode of inheritance	Affected protein	OMIM No.	Subtype
22.5	Adenosine kinase deficiency	Hypermethioninemia due to adenosine kinase deficiency	ADK	*ADK*	10q22.2	AR	Adenosine kinase	614300	All forms
22.6	Cystathionine beta-synthase deficiency	Classical homocystinuria	CBS	*CBS*	21q22.3	AR	Cystathionine beta-synthase	263200	All forms
22.7	Cystathionase deficiency	Cystathionine gamma-lyase deficiency	CTH	*CTH*	1p31.1	AR	Cystathionine gamma-lyase	219500	All forms (probably benign)
22.8	Methanethiol oxidase deficiency	Extraoral halitosis, MTO deficiency	MTO	*SELENBP1*	1q21.3	AR	Methanethiol oxidase	604188	All forms
22.9	Sulfite oxidase deficiency	Isolated sulfite oxidase deficiency	SUOX	*SUOX*	12q13.13	AR	Sulfite oxidase	272300	Isolated
22.10	Mitochondrial sulfur dioxygenase deficiency	Ethylmalonic encephalopathy	ETHE1	*ETHE1*	19p13.32	AR	Mitochondrial persulfide dioxygenase	602473, 608451	All forms
22.11	Mercaptopyruvate sulfur transferase deficiency	β-Mercaptolactate cysteine disulfiduria	MPST	*MPST*	22q12.3	AR	Mercaptopyruvate sulfur transferase	602496	All forms (probably benign)

[a]Inheritance of this risk factor with incomplete penetrance is autosomal dominant

Metabolic Pathway

Metabolism of sulfur amino acids is summarized in Fig. 22.1. Methionine and homocysteine are linked by the remethylation cycle (see Chap. 28 for details) and the transsulfuration pathway. The essential amino acid methionine is derived from the diet or catabolism of proteins. Methionine is first converted to *S*-adenosylmethionine by two methionine *S*-adenosyltransferases, the ubiquitously expressed MATII and liver-expressed MATI/III encoded by *MAT2A* and *MAT1A* genes, respectively. *S*-adenosylmethionine (AdoMet) is the methyl-group donor in a wide range of transmethylation reactions including DNA methylation, creatine, and neurotransmitter synthesis, and surplus amounts are converted to sarcosine by glycine *N*-methyltransferase. The transfer of methyl groups from AdoMet yields *S*-adenosylhomocysteine, which is a strong inhibitor of transmethylation reactions and must be cleaved to adenosine and homocysteine by *S*-adenosylhomocysteine hydrolase. Depending on a number of factors, about half of available homocysteine is recycled into methionine by the folate and cobalamin-dependent remethylation cycle, while the other half is channeled into the transsulfuration pathway. In the latter series of reactions, homocysteine is condensed with serine to form cystathionine via a reaction catalyzed by the pyridoxal phosphate-requiring cystathionine ß-synthase. Cystathionine is cleaved to cysteine, α-ketobutyrate, and ammonia by another pyridoxal phosphate-dependent enzyme, γ-cystathionase. Cysteine is an important precursor for the synthesis of glutathione and taurine and the major source for endogenous production of the signaling molecule hydrogen sulfide. The sulfur atom of cysteine can be fully oxidized to sulfate via two major pathways. Cysteine can be converted to cysteine sulfinic acid by cysteine dioxygenase followed by transamination with α-oxoglutarate yielding pyruvate and sulfite, although cysteine sulfinate can be also decarboxylated and give rise to hypotaurine and finally to taurine. The other pathway utilizes cysteine for the synthesis of the gasotransmitter hydrogen sulfide by catalysis of CBS, CTH, MPST, and cysteinyl-tRNA synthetase; hydrogen sulfide exists in a dynamic equilibrium of dissolved gas, hydrosulfide, and various organic and inorganic polysulfides. Oxidation of hydrogen sulfide occurs in mitochondria and starts with persulfidation of GSH by sulfide:quinone oxidoreductase, followed by release of sulfite under the catalysis of ETHE1. Sulfite is finally oxidized by the molybdenum cofactor-containing sulfite oxidase to the ultimate oxidation product sulfate.

Signs and Symptoms

Table 22.1 Methionine adenosyltransferase I/III deficiency (AR and AD[a] forms)

System	Symptoms and biomarkers	Neonatal (birth–1 month)	Infancy (1–18 months)	Childhood (1.5–11 years)	Adolescence (11–16 years)	Adulthood (>16 years)
CNS	Cognitive dysfunction			±	±	±
	Demyelination			±	±	±
	Developmental delay			±	±	±
	Dysdiadochokinesis			±	±	±
	Dysmetria			±	±	±
	Dystonia			±	±	±
	Headache			±	±	±
	Language difficulties			±	±	±
	Tendon reflexes, increased			±	±	±
	Tremor			±	±	±
	Vacuolating myelopathy			**±**	**±**	**±**
Eye	Nystagmus			±	±	±
Other	**Cabbage-like breath odor (dimethylsulfide)**	**±**	**±**	**±**	**±**	**±**
Laboratory findings	Cystathionine (plasma)	n	n	n	n	n
	Homocysteine, total (plasma)	n-↑	n-↑	n-↑	n-↑	n-↑
	Methionine (P, U)	↑↑↑	↑↑↑	↑↑↑	↑↑↑	↑↑↑
	Methionine sulfoxide (urine)	↑	↑	↑	↑	↑
	Methionine-to-cystathionine ratio	↑↑	↑↑	↑↑	↑↑	↑↑
	Methionine-to-total homocysteine ratio	↑↑	↑↑	↑↑	↑↑	↑↑
	S-Adenosylhomocysteine (plasma)	n	n	n	n	n
	S-Adenosylmethionine (plasma)	n	n-↓	n-↓	n-↓	n-↓

[a]The only reported clinical abnormality in autosomal dominant MATI/III deficiency is the cabbage-like odor

Table 22.2 Methionine adenosyltransferase II deficiency

System	Symptoms and biomarkers	Neonatal (birth–1 month)	Infancy (1–18 months)	Childhood (1.5–11 years)	Adolescence (11–16 years)	Adulthood (>16 years)
Cardiovascular	**Thoracic aortic aneurysms**					±

There are no specific biochemical abnormalities in individuals with thoracic aortic aneurysms who are heterozygotes for *MAT2A* mutations

Table 22.3 Glycine *N*-methyltransferase deficiency

System	Symptoms and biomarkers	Neonatal (birth–1 month)[a]	Infancy (1–18 months)[a]	Childhood (1.5–11 years)	Adolescence (11–16 years)	Adulthood (>16 years)
Digestive	Hepatomegaly		±	±		
Other	Failure to thrive		±			
Laboratory findings	ALAT (P)			↑		
	ASAT (P)			↑		
	Homocysteine, total (P)			n-↑	n-↑	n-↑
	Methionine (P, U)			↑↑↑	↑↑↑	↑↑↑
	S-Adenosylhomocysteine (P)			n	n	n
	S-Adenosylmethionine (P)			↑↑↑	↑↑↑	↑↑↑
	Sarcosine (P)			n	n	n

[a]Metabolite levels not yet reported in these age groups, however, expected to be similar to other age groups

Table 22.4 *S*-adenosylhomocysteine hydrolase deficiency

System	Symptoms and biomarkers	Neonatal (birth–1 month)	Infancy (1–18 months)	Childhood (1.5–11 years)	Adolescence (11–16 years)	Adulthood (>16 years)
CNS	Cerebellar hypoplasia	±	±			
	Delayed myelination	±	±	±		
	Developmental delay	**±-+++**	**+-+++**	**+**	**±**	**±**
	Hypoplasia of corpus callosum	±	±			
	Hypoplasia of pons	±	±			
Digestive	Hepatocellular carcinoma					±
	Liver dysfunction	±-+++	±-+++	±	±	±
Eye	Strabismus	±	±	±	±	–
Hematological	Coagulopathy	**±-+++**	**±-+++**	**±-++**	**±**	**±**
Metabolic	Protein synthesis reduced	±-+++	±-+++	±	–	–
Musculoskeletal	Absent tendon reflexes	+	+	+	+	+
	Muscle weakness	**+-+++**	**+-+++**	**+-++**	**+-++**	**++**
	Myopathy	**+-+++**	**+-+++**	**++**	**++**	**++**
	Weak tendon reflexes	++-+++	++-+++	++-+++	++-+++	++-+++
Psychiatric	Attention deficit disorder		±	±-++	±-++	±-+++
	Behavior, aggressive			±	±	±
	Hyperactivity			±	±	±
Respiratory	Respiratory insufficiency	±-+++	±-+++			
Other	Fetal hydrops	±-++				
Laboratory findings	ALAT (plasma)	n-↑↑	↑-↑↑	↑-↑↑	↑-↑↑	↑-↑↑
	Albumin (serum)	↓↓↓-n	↓↓↓-n	↓↓↓-n	↓↓↓-n	↓↓↓-n
	ASAT (plasma)	n-↑↑	↑-↑↑	↑-↑↑	↑-↑↑	↑-↑↑
	Creatine kinase (plasma)	↑-↑↑	↑-↑↑	↑↑	↑↑	↑↑
	Homocysteine, total (plasma)	n-↑	n-↑	n-↑	n-↑	n-↑
	Methionine (plasma and urine)	n-↑↑	n-↑↑	n-↑↑	n-↑↑	n-↑↑
	Prothrombin time	n-↑↑	n-↑↑	n-↑↑↑	n-↑↑	n-↑↑
	S-Adenosylhomocysteine (plasma)	↑↑↑	↑↑↑	↑↑↑	↑↑↑	↑↑↑
	S-Adenosylmethionine (plasma)	↑↑↑	↑↑↑	↑↑↑	↑↑↑	↑↑↑
	Sarcosine (plasma)	n-↑	n-↑	n-↑	n-↑	n-↑

Table 22.5 Adenosine kinase deficiency

System	Symptoms and biomarkers	Neonatal (birth–1 month)[a]	Infancy (1–18 months)[a]	Childhood (1.5–11 years)	Adolescence (11–16 years)	Adulthood (>16 years)
Cardiovascular	Cardiac anomalies, malformations	±	±	±	±	±
CNS	Epilepsy		±	±-++	±-++	±-++
	Developmental delay		++-+++	++-+++	++-+++	++-+++
	Hypotonia	±-++	+-++	+-++	+-++	+-++
	Thin corpus callosum	±	±	±	±	±
Digestive	Cholestasis	±	±	±	±	±
	Liver dysfunction	±	±	±	±	±
	Liver steatosis	±	+	+	+	+
Ear	Hearing loss, sensorineural	–	±-++	±-++	±-++	±-++
Musculoskeletal	Macrocephaly		±-++	±-++	±-++	±-++
	Frontal bossing		+	+	+	+
	Muscle weakness, progressive		±-+	±-++	±-++	±-++
	Short stature	±	±	±	±	±
	Slender hands and feet	±	±	±	±	±
Other	Failure to thrive	±	±	±	±	±
Laboratory findings	Adenosine (dried blood spots)			n-↑	n-↑	n-↑
	Adenosine (urine)			n-↑	n-↑	n-↑
	ALAT (plasma)	↑-↑↑	n-↑↑	n-↑↑	n-↑↑	n-↑↑
	Bilirubin, conjugated (plasma)	↑	↑			
	Creatine kinase (plasma)	n-↑	n-↑	n-↑	n-↑	n-↑
	Glucose (plasma)	n-↓	n-↓	n-↓	n-↓	
	Homocysteine, total (plasma)	n-↑	n-↑	n-↑	n-↑	n-↑
	Methionine (plasma and urine)	n-↑↑↑	n-↑↑↑	n-↑↑↑	n-↑↑↑	n-↑↑↑
	Prothrombin time	n-↑	n-↑	n-↑	n-↑	n-↑
	S-Adenosylhomocysteine (plasma)			↑-↑↑	↑-↑↑	↑-↑↑
	S-Adenosylmethionine (plasma)			↑-↑↑	↑-↑↑	↑-↑↑
	Uric acid (plasma)		n-↑	n-↑↑	n-↑↑	n-↑

[a]Metabolite levels not yet reported in these age groups, however, expected to be similar to other age groups

Table 22.6 Cystathionine beta-synthase deficiency

System	Symptoms and biomarkers	Neonatal (birth–1 month)	Infancy (1–18 months)	Childhood (1.5–11 years)	Adolescence (11–16 years)	Adulthood (>16 years)
Cardiovascular	Thromboses, infarcts		±	±	±	±
CNS	Developmental delay		n-±	n-+++	n-+++	n-+++
	Intellectual disability			n-+++	n-+++	n-+++
	Psychiatric symptoms			±	±	±
	Seizures		±	±	±	±
	Stroke		±	±	±	±
Dermatological	Malar flush			±	±	±
Eye	Ectopia lentis		±	±	±	±
	Iridodonesis		±	±	±	±
	Myopia		±	±	±	±
Hematological	Thromboembolism		±	±	±	±
Musculoskeletal	Arachnodactyly			±	±	±
	Genu valgum			±	±	±
	Kyphosis			±	±	±
	Marfanoid features			±	±	±
	Osteoporosis		±	±	±	±
	Pes cavus			±	±	±
	Scoliosis			±	±	±
	Sternal deformities			±	±	±
Laboratory findings	Cystathionine by LC-MS/MS or GC-MS/MS (plasma)	n-↓↓	n-↓↓	n-↓↓	n-↓↓	n-↓↓
	Cysteine, total (plasma)	↓↓	↓↓	↓↓	↓↓	↓↓
	Cystine (plasma)	↓↓	↓↓	↓↓	↓↓	↓↓
	Homocystine (plasma, urine)	↑-↑↑	↑-↑↑	↑-↑↑	↑-↑↑	↑-↑↑
	Homocysteine, total (DBS)	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑
	Homocysteine, total (plasma)	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑
	Methionine (DBS)	n-↑↑	n-↑↑	n-↑↑	n-↑↑	n-↑↑
	Methionine (plasma)	n-↑↑	n-↑↑	n-↑↑	n-↑↑	n-↑↑
	Methionine-to-cystathionine ratio	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑	↑-↑↑↑
	Methionine-to-phenylalanine ratio (DBS)	n-↑↑	n-↑↑	n-↑↑	n-↑↑	n-↑↑
	Methionine-to-total homocysteine ratio	↓	↓	↓	↓	↓
	Nitroprusside test (urine)		↑	↑	↑	↑
	S-Adenosylhomocysteine (plasma)	↑-↑↑	↑-↑↑	↑-↑↑	↑-↑↑	↑-↑↑
	S-Adenosylmethionine (plasma)	↑↑	↑↑	↑↑	↑↑	↑↑
	Sarcosine (plasma)	↑-↑↑	↑-↑↑	↑-↑↑	↑-↑↑	↑-↑↑

Table 22.7 Cystathionase deficiency

System	Symptoms and biomarkers	Neonatal (birth–1 month)	Infancy (1–18 months)	Childhood (1.5–11 years)	Adolescence (11–16 years)	Adulthood (>16 years)
Other	No clinical significance	+	+	+	+	+
Laboratory findings	Cystathionine (plasma)	↑	↑	↑	↑	↑
	Cystathionine (urine)	↑↑	↑↑	↑↑	↑↑	↑↑
	Cystathionine by GC-MS or LC-MS/MS (plasma)	↑↑↑	↑↑↑	↑↑↑	↑↑↑	↑↑↑
	Cystathionine by GC-MS or LC-MS/MS (urine)	↑↑↑	↑↑↑	↑↑↑	↑↑↑	↑↑↑
	Cysteine, total (plasma)	n	n	n	n	n
	Homocysteine, total (plasma)	n-↑	n-↑	n-↑	n-↑	n-↑
	Methionine-to-cystathionine ratio	↓↓	↓↓	↓↓	↓↓	↓↓

Table 22.8 Methanethiol oxidase deficiency

System	Symptoms and biomarkers	Neonatal (birth–1 month)[a]	Infancy (1–18 months)[a]	Childhood (1.5–11 years)	Adolescence (11–16 years)	Adulthood (>16 years)
Other	Cabbage-like smelling breath	**±-+**	**±-+**	**±-+**	**±-+**	**±-+**
Laboratory findings	Dimethylsulfide (breath, blood)			↑↑	↑↑	↑↑
	Dimethylsulfoxide (blood)			↑↑	↑↑	↑↑
	Methanethiol (breath)			↑↑	↑↑	↑↑

[a]Metabolite levels not yet reported in these age groups, however, expected to be similar to other age groups

Table 22.9 Sulfite oxidase deficiency

System	Symptoms and biomarkers	Neonatal (birth–1 month)	Infancy (1–18 months)	Childhood (1.5–11 years)	Adolescence (11–16 years)	Adulthood (>16 years)[a]
CNS	Acute hemiplegia			±	±	±
	Axial hypotonia	±	+	+	±	±
	Cerebellar atrophy (MRI)	±	+	+	+	+
	Cerebral atrophy (MRI)	±	+	+	+	+
	Cystic white matter changes	±	+	+	+	+
	Microcephaly	±	+	+	+	+
	Movement, abnormal	±	+	+	+	+
	Peripheral hypertonia	±	+	+	±	±
	Retardation, psychomotor	±-+++	+-+++	+-+++	+-+++	+-+++
	Seizures, pharmacoresistant	±-+++	±-+++	±-+++	±-+++	±-+++
	Ventriculomegaly (brain)	±	+	+	+	+
Digestive	Feeding difficulties	±-+	±-+	±-+	±-+	±-+
Eye	Ectopia lentis		±	±	±	±
Laboratory findings	Alpha-aminoadipic semialdehyde (cerebrospinal fluid)	↑	↑	↑		
	Alpha-aminosemialdehyde (urine)	↑	↑	↑		
	Homocysteine, total (plasma)	↓	↓	↓	↓	↓
	Methionine (plasma)	n	n	n	n	n
	Pipecolic acid (cerebrospinal fluid)	↑	↑	↑		
	Pyridoxal 5′-phosphate (cerebrospinal fluid)	↓	↓	↓		
	S-Sulfocysteine (plasma)	↑-↑↑	↑-↑↑	↑-↑↑	↑-↑↑	↑-↑↑
	S-Sulfocysteine (urine)	↑-↑↑	↑-↑↑	↑-↑↑	↑-↑↑	↑-↑↑
	Sulfite (plasma, urine)	↑-↑↑	↑-↑↑	↑-↑↑	↑-↑↑	↑-↑↑
	Taurine (plasma, urine)	↑-↑↑	↑-↑↑	↑-↑↑	↑-↑↑	↑-↑↑
	Thiosulfate (plasma, urine)	↑↑	↑↑	↑↑	↑↑	↑↑
	Uric acid (plasma)	n	n	n	–	–
	Uric acid (urine)	n	n	n	–	–

[a]Data on patients who are alive after age of 16 years are so scarce that the information in that column is only extrapolation from the column of the previous age group

Table 22.10 Mitochondrial sulfur dioxygenase deficiency

System	Symptoms and biomarkers	Neonatal (birth–1 month)[a]	Infancy (1–18 months)	Childhood (1.5–11 years)	Adolescence (11–16 years)	Adulthood (>16 years)
Cardiovascular	Orthostatic acrocyanosis		**±-+++**	**±-+++**	**±-+++**	
CNS	Axial hypotonia	±-++	+-+++	+-+++	+-+++	
	Dystonia		+-++	+-++	+-++	
	Hyperintense lesions in the basal ganglia on MRI (Leigh-like encephalopathy)		+-+++	+-+++		
	Hyperintense patchy T2 changes on MRI in the white matter, brain stem and cerebellum		±-+++	±-+++		
	Retardation, psychomotor		+++	+++	+++	
	Seizures		+-++	+-++	+-++	
	Spastic tetraplegia		+++	+++	+++	
Dermatological	Petechiae		**±-+++**	**±-+++**	**±-+++**	
Digestive	Hemorrhagic diarrhea, chronic		**+-+++**	**+-+++**	**+-+++**	
Metabolic	Hematuria		+	+	+	
Other	Failure to thrive		+-+++	+-+++	+-+++	
Laboratory findings	2-Methylbutyrylglycine (urine)		↑↑	↑↑		
	C4 Butyrylcarnitine (plasma, DBS)	↑↑	↑↑	↑↑		
	C4 Isobutyrylcarnitine (plasma, DBS)		↑	↑		
	C5 2-Methylbutyrylcarnitine (plasma, DBS)		↑	↑		
	C5 Isovalerylcarnitine (plasma, DBS)		↑	↑		
	C5-DC Glutarylcarnitine (plasma, DBS)	↑↑	↑↑	↑↑	↑↑	↑↑
	Ethylmalonic acid (urine)	↑↑	↑↑↑	↑↑↑		
	Hydrogen sulfide (plasma)	↑-↑↑	↑-↑↑	↑-↑↑		
	Isovalerylglycine (urine)		↑	↑		
	Lactate (plasma)		↑↑	↑↑		
	Methylsuccinic acid (urine)		↑↑	↑↑		
	S-sulfocysteine (urine)		n-↑	n-↑		
	Sulfite (plasma, urine)	↑↑	↑↑	↑↑		
	Taurine (plasma, urine)		↑	↑		
	Thiosulfate (plasma, urine)		↑↑↑	↑↑↑		

Milder course with less expressed neurological signs and symptoms, lack of vascular symptoms, and survival in adulthood is very exceptional. To avoid confusion with much more frequent severe course, this milder form of the disease was not the basis for symbols entered in the table

[a]Metabolite levels not yet reported in these age groups, however, expected to be similar to other age groups

Table 22.11 Mercaptopyruvate sulfur transferase deficiency

System	Symptoms and biomarkers	Neonatal (birth–1 month)[a]	Infancy (1–18 months)[a]	Childhood (1.5–11 years)	Adolescence (11–16 years)	Adulthood (>16 years)
CNS	Intellectual disability				±	±
Laboratory findings	Beta-mercaptolactate cysteine disulfide (urine)				↑	
	Mercaptopyruvate (urine)					↑
	Mercaptolactate (urine)					↑
	Nitroprusside test (urine)				↑	↑

[a]Metabolite levels not yet reported in these age groups, however, expected to be similar to other age groups

Reference Values[a]

Analyte	Infant <1 year	Child 1–12 years	Adolescent 12–18 years	Adult >18 years
Plasma amino acids (μmol/L)				
Methionine	12–31	11–30	16–23	15–40
Homocystine	Below detection limit (approx. 5 μmol/L)			
Cystathionine	Below detection limit (approx. 5 μmol/L)			
Taurine	15–200	19–139	10–162	6–126
S-sulfocysteine	Below detection limit (approx. 5 μmol/L)			
Special assays in plasma or blood (in blood where indicated in brackets) (μmol/L)				
Total homocysteine	3.5–10	4–10	4–13	5–15
Total cysteine	200–360 (not age stratified)			
Sarcosine	0.6–2.5 (not age stratified)			
S-adenosylmethionine	0.03–0.16 (not age stratified)			
S-adenosylhomocysteine	0.015–0.06 (not age stratified)			
Cystathionine (by sensitive GC-MS or LC-MS/MS assays)	0.08–0.5 (up to 1 in neonates)			
Methionine-to-cystathionine ratio	40–200 (not age stratified)			
Thiosulfate	0.4–0.7 (not age stratified)			
Sulfite	0.2–0.5 (not age stratified)			
Free sulfide (hydrogen sulfide)	0.15–0.3 (not age stratified)			
Dimethylsulfide (blood)	<0.007 (not age stratified)			
Dimethylsulfoxide (blood)	<1 (not age stratified)			
Lactate (blood)	Reference ranges for lactate in blood are shown in Chap. 42 of this book			
Dried blood spots (μmol/L blood)				
Methionine	7–40 (not age stratified)			
Methionine/phenylalanine	0.15–0.6			
Total homocysteine	2.5–9		5.5–9	8–13
Methionine-to-total homocysteine ratio	2–4 (not age stratified)			
Reference ranges for acylcarnitines in dried blood spots are shown in Chap. 5 of this book				
Urinary amino acids (mmol/mol creatinine)				
Methionine	7–29	5–20	3–17	2–16
Cystathionine	Usually below detection limit (not age stratified)			
Homocystine	0.2–3.7 (not age stratified)			
Reference ranges for organic acids in urine are shown in Chap. 4 of this book				
Urinary special assays (mmol/mol creatinine)				
Total cysteine	10–50 (not age stratified)			
Total homocysteine	1–4 (not age stratified)			
Thiosulfate	0.8–2.5 (not age stratified)			
Sulfite	0.03–0.15 (not age stratified)			
S-sulfocysteine	0.3–1 (not age stratified)			
Simple tests in urine (qualitative test)				
Nitroprusside test	Negative (not age stratified)			
Exhaled air (ppb)				
Dimethylsulfide	1–19 (not age stratified)			
Methanethiol	0.01–0.24 (not age stratified)			

[a]Table shows typical values from literature (Duran et al. 2008, Chap. 2 of this book) and authors' laboratories; due to the lack of harmonization and the use of different analytical platforms for many of the metabolites listed, these reference ranges are not universally applicable. Therefore, it is important to use the reference ranges given by the laboratory which issued the results. Reference ranges can be also found in the Human Metabolome Database (see Sect. 22.17 Online Resources)

Pathological Values[a,b,c]

Metabolites	22.1[b] MAT I/III	22.3 GNMT	22.4 SAHH	22.5 ADK	22.6 CBS	22.7 CTH	22.8 MTO	22.9 SUOX	22.10 ETHE1	22.11 MPST
Plasma amino acids										
Methionine	↑↑↑	↑↑↑	n-↑↑	n-↑↑↑	n-↑↑↑	n	n			
Homocystine					↑-↑↑↑					
Cystathionine						↑				
Taurine								↑-↑↑	↑	
S-sulfocysteine								↑-↑↑		
Plasma acylcarnitines										
C4 butyrylcarnitine									↑↑	
C4 isobutyrylcarnitine									↑	
C5 2-methylbutyrylcarnitine									↑	
C5 isovalerylcarnitine									↑	
Glutarylcarnitine									↑	
Special assays in plasma or blood (in blood where indicated in brackets)										
Total homocysteine	n-↑	n-↑	n-↑	n-↑	↑-↑↑↑	n-↑		↓	n-↓	
Total cysteine					↓↓	n		↓		
Sarcosine	n-↑	n	n-↑		↑-↑↑					
S-adenosylmethionine	n-↓	↑↑↑	↑↑↑	↑-↑↑	↑↑					
S-adenosylhomocysteine			↑↑↑	↑-↑↑	↑-↑↑					
Cystathionine (by sensitive GC-MS or LC-MS/MS assays)					n-↓↓	↑↑↑				
Methionine-to-cystathionine ratio	↑↑				↑-↑↑↑	↓↓				
Thiosulfate								↑↑	↑↑	
Sulfite								↑↑	↑↑	
Free sulfide (hydrogen sulfide)								↑	↑↑	
Lactate (blood)									↑	
Dimethylsulfoxide (blood)							↑↑			
Dimethylsulfide (blood)							↑↑			
Dried blood spots										
Methionine	↑↑-↑↑↑				n-↑↑					
Methionine/phenylalanine	↑↑-↑↑↑				n-↑↑					
Total homocysteine	n				↑-↑↑↑					
Methionine-to-total homocysteine	↑↑				↓					
Adenosine				n-↑						
C4 butyrylcarnitine									↑↑	
C4 isobutyrylcarnitine									↑	
C5 2-methylbutyrylcarnitine									↑	
C5 isovalerylcarnitine									↑	
Glutarylcarnitine									↑	
Urinary amino acids										
Methionine	↑↑↑	↑↑↑	n-↑↑	↑↑	n-↑↑					
Cystathionine					n-↓	↑↑				
Homocystine					↑-↑↑↑					
Organic acids in urine										
Ethylmalonic acid									↑↑-↑↑↑	
2-Methylbutyrylglycine									↑↑	
Methylsuccinic acid									↑↑	
Isovalerylglycine									↑	
Urinary special assays										
Total homocysteine					↑-↑↑↑	n-↑				
Thiosulfate								↑↑↑	↑↑	
Sulfite								↑↑↑	↑↑	
S-sulfocysteine								↑-↑↑	n-↑	
Adenosine				n-↑						

Metabolites	22.1[b] MAT I/III	22.3 GNMT	22.4 SAHH	22.5 ADK	22.6 CBS	22.7 CTH	22.8 MTO	22.9 SUOX	22.10 ETHE1	22.11 MPST
Alpha-aminosemialdehyde								↑		
Mercaptolactate, mercaptopyruvate										↑↑
Mercaptocysteine disulfide										↑↑
Simple tests in urine										
Nitroprusside test[d]					Positive					Positive
Exhaled air										
Dimethylsulfide						↑↑				
Methanethiol						↑↑				
Special assays in cerebrospinal fluid										
Pipecolic acid								↑		
Pyridoxal 5′-phosphate								↓		

[a]Pathological values may vary in different age groups and disease forms; for details, see Tables 22.1–22.11
[b]There are no specific biochemical abnormalities in individuals with thoracic aortic aneurysms who are heterozygotes for *MAT2A* mutations. Therefore, related column is not provided
[c]Normal values are denoted by "n" only when particularly important for differential diagnosis. Blank cells indicate that the metabolite is within reference range or that data are not available
[d]Nitroprusside test has limited reliability due to false-negative results

Diagnostic Flowcharts

Since most of the mentioned diseases are at least partly treatable if diagnosed early and may have rapid course, the *diagnostic work-up* in suspected cases should also be rapid. Suspicion should be raised in all patients having unexplained neurological symptoms, muscle disease, liver disease, lens dislocation and other marfanoid features, orthostatic acrocyanosis, or any other symptom attributable to diseases from this group or unexplained hypermethioninemia and/or hyperhomocysteinemia or hypohomocysteinemia (see Sect. 22.4). Measurement of plasma total homocysteine and amino acids (methionine, taurine, and *S*-sulfocysteine) and special tests for sarcosine, cystathionine, *S*-adenosylmethionine, and *S*-adenosylhomocysteine should be sufficient as the first step to detect all diseases from this group; sulfite and thiosulfate analysis is necessary for diagnosing disorders in the distal part of transsulfuration pathway (for differential diagnosis of hypermethioninemia and hypo- and hyperhomocysteinemia, see Diagnostic flowcharts, Figs. 22.2 and 22.3).

It is useful to keep in mind that in MAT I/III deficiency homocysteine can be sufficiently elevated to mimic CBS deficiency, probably due to less than normal stimulation of CBS by low AdoMet and inhibition of betaine-homocysteine methyltransferase, N^5-*methyltetrahydrofolate-homocysteine* methyltransferase and cystathionine gamma-lyase by methionine, in particular in patients with very high methionine values (Stabler et al. 2002). Mild elevations of tHcy, which can be diagnostically misleading, have also been described in other methylation defects and in CTH deficiency.

Pyridoxine responsiveness test in CBS deficiency. This test is performed in patients with CBS deficiency to assess pyridoxine responsiveness. Recent guidelines recommended standard tests in patients detected symptomatically using 10 mg/kg/day pyridoxine (maximum of 500 mg/day) for 6 weeks; the plasma tHcy concentration should be measured at least twice before treatment and twice on treatment (by the end of weeks 2 and 6). The test should be done on normal protein intake, folate supplements should be given, and vitamin B_{12} deficiency should be corrected prior to testing. Classification of pyridoxine responsiveness is as follows: full responsiveness, plasma tHcy levels below 50 μmol/L; extreme responsiveness, tHcy below 50 μmol/L on pyridoxine doses <1 mg/kg/day; partial responsiveness, tHcy falls >20% of pre-test average but above 50 μmol/L; and non-responsiveness, tHcy falls by <20% (Morris et al. 2017).

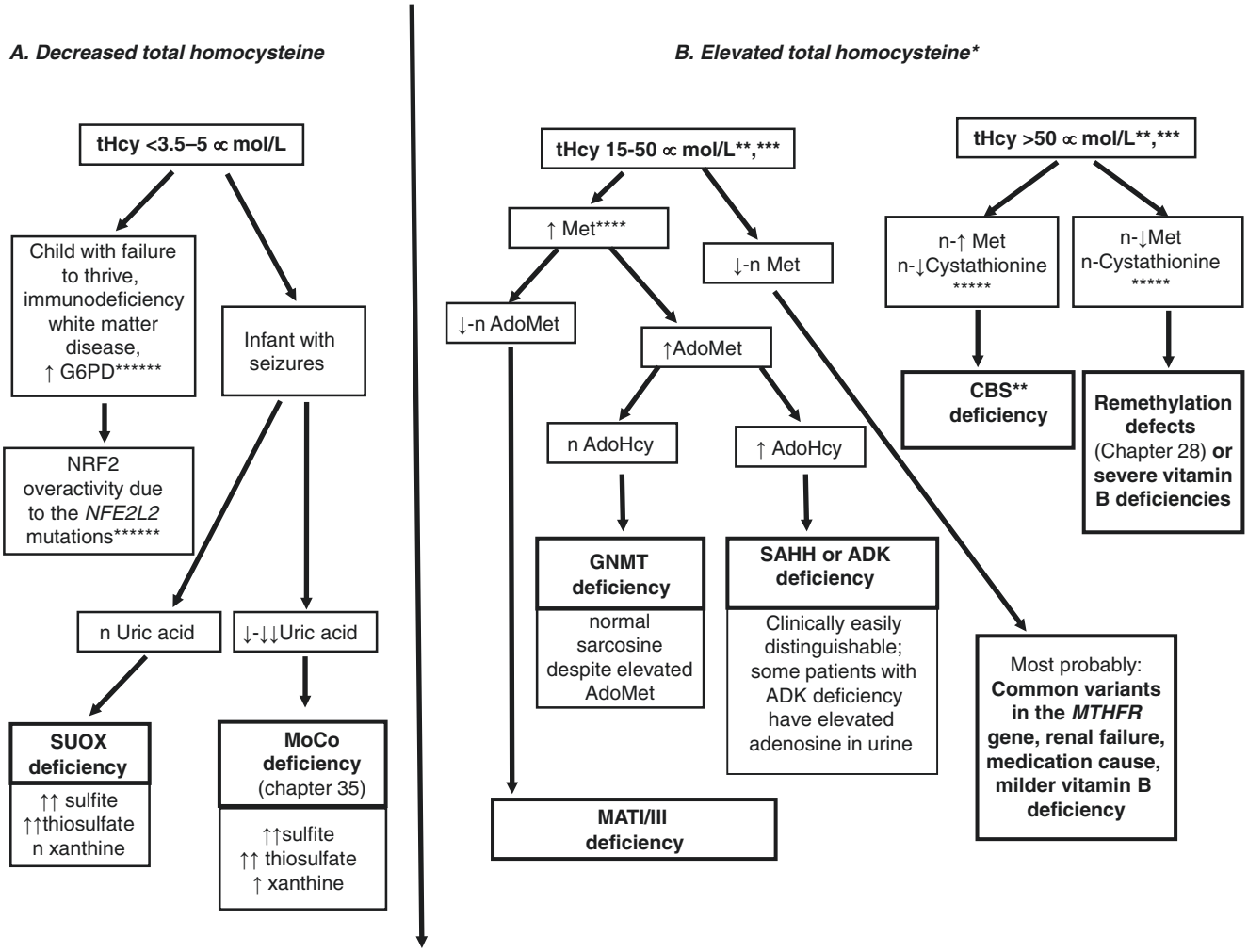

Fig. 22.2 Diagnostic flowchart for hypo- (**a**) and hyperhomocysteinemia (**b**). * tHcy range of 5–15 μmol/L is used here as reference range for all ages; actually, in children the upper limit of reference range is lower (see Reference Values). ** In non-treated CBS deficiency, tHcy is usually significantly >50 μmol/L but may be lower in mild cases, in particular when on vitamin supplementation (even non-pharmacological doses of pyridoxine). *** In non-CBS hypermethioninemias, tHcy is usually normal or only mildly elevated, and values of about 50 μmol/L are exceptionally seen. **** In ADK and SAHH deficiency, plasma methionine concentrations can occasionally be normal, for instance, in SAHH deficiency in early infancy during lower methionine intake and higher needs for growth. ***** Cystathionine for differential diagnosis of hyperhomocysteinemia cannot be detected by amino acid analyzers and must be determined by sensitive GC-MS or LC-MS/MS assay. ****** This disease has been reported in only few patients (for details, see Chap. 16), and all abnormalities are not necessarily present in all patients. Mild hypohomocysteinemia (below 3.5–5 μmol/L) is sometimes seen without association with a particular disease. *ADK* adenosine kinase, *AdoHcy* *S*-adenosylhomocysteine, *AdoMet* *S*-adenosylmethionine, *CBS* cystathionine beta synthase, *GNMT* glycine *N*-methyltransferase, *G6PD* glucose-6-phosphate dehydrogenase, *MAT I/III* methionine adenosyltransferase I/III, *Met* methionine, *MoCo* molybdenum cofactor, *MTHFR* methylenetetrahydrofolate reductase, *NFE2L2* nuclear factor, erythroid 2 like 2, *NRF2* nuclear factor-erythroid 2-related factor 2, *SAHH* *S*-adenosylhomocysteine hydrolase, *SUOX* sulfite oxidase, *tHcy* plasma total homocysteine

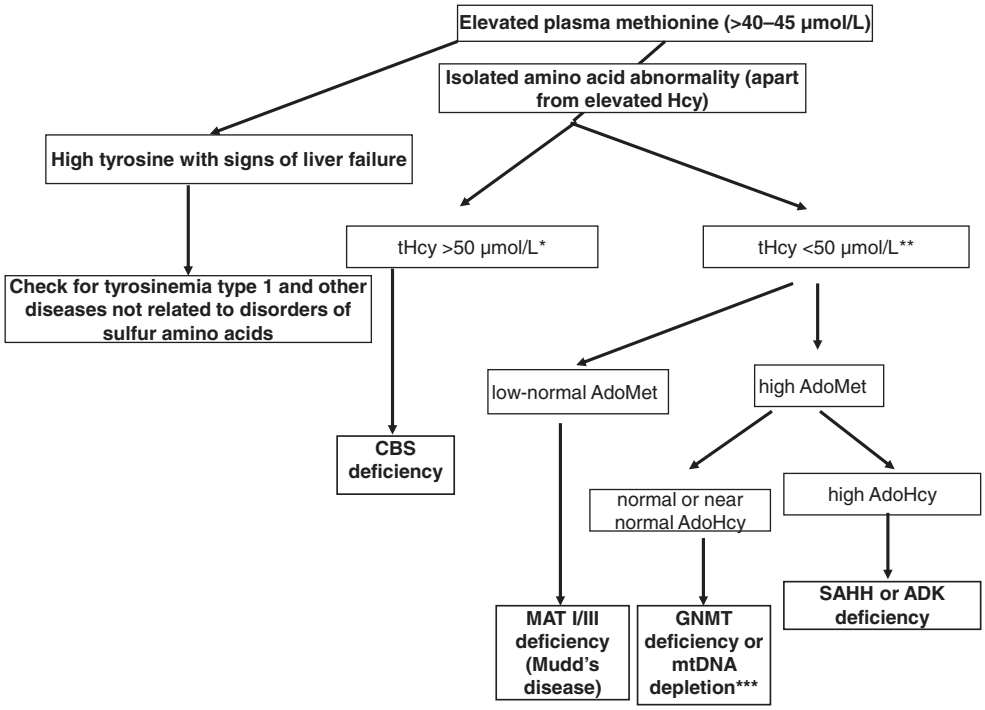

Fig. 22.3 Diagnostic flowchart in patients with hypermethioninemia. *In untreated CBS deficiency, tHcy is usually >50 µmol/L but may be lower in mild cases, in particular when on vitamin supplementation (non-pharmacological doses). **In non-CBS deficiency hypermethioninemias, tHcy is usually normal or only mildly elevated, and values of about 50 µmol/L are rarely seen. ***Tyrosine can be elevated. *ADK* adenosine kinase, *AdoHcy* *S*-adenosylhomocysteine, *AdoMet* *S*-adenosylmethionine, *CBS* cystathionine beta synthase, *GNMT* glycine *N*-methyltransferase, *MAT I/III* methionine adenosyltransferase I/III, *mtDNA* mitochondrial DNA, *SAHH* *S*-adenosylhomocysteine hydrolase, *tHcy* plasma total homocysteine

Loading Test

Increase of plasma dimethylsulfone and dimethylsulfoxide in methionine loading test in patients suspected to suffer from extraoral halitosis due to methanethiol oxidase deficiency can point to the cause of the disease. The methionine loading test became obsolete in diagnosis of sulfur-containing amino acids disorders.

Specimen Collection

Overview on required samples for metabolite, enzyme, and mutation analysis

Disorder	Metabolite: sample
	Amino acids (including taurine): plasma or serum[a] and urine
	Organic acids: urine
	Acylcarnitines: dried blood spots and plasma/serum
	Special assays
CBS, CTH, SUOX	Total homocysteine and total cysteine: plasma[b] and urine
MATI/III, GNMT, ADK, CBS	*S*-adenosylmethionine: plasma[c], whole blood
MATI/III, GNMT, ADK, CBS	*S*-adenosylhomocysteine: plasma[c], whole blood
SUOX, ETHE	Thiosulfate: plasma and urine[d,e]
SUOX, ETHE	Sulfite: plasma and urine[d,e]
SUOX, ETHE	Free sulfide (hydrogen sulfide): plasma[d]
MTO	Methanethiol and dimethylsulfide in exhaled air
CBS	Methionine, Met/Phe and tHcy in dried blood spots
	Other assays: plasma, blood or urine (may require special sampling conditions, consult the laboratory)
	Enzyme assays[f]: specimen
MAT I/III	Liver[g]
GNMT	Liver[g]
SAHH	Cultured fibroblasts, erythrocytes, liver
ADK	Not available
CBS	Cultured fibroblasts and plasma[a]
CTH	Liver[g]
SUOX	Cultured fibroblasts
ETHE1	Not available
MPST	Erythrocytes
MTO	Erythrocytes

Disorder	Metabolite: sample
	Mutation analysis
All disorders	DNA

[a]Blood for plasma amino acids analysis should be sampled after 3–4 h fasting. For taurine determination only plasma should be used and handled as in [b]. Rapid deproteinization is essential for determination of non-protein bound homocysteine (this analysis is considered obsolete and should be replaced by total homocysteine determination)
[b]Samples should be immediately placed into ice/water slush, separation of plasma within 60 min since collection is essential
[c]EDTA blood on ice, immediate separation of plasma and deproteinization (within 30 min since collection)
[d]Plasma: only lithium heparin plasma should be collected, samples should be immediately placed into ice/water slush, separation of plasma within 15 min since collection, and immediate freezing prior to analysis at −85 °C is essential
[e]Urine: only freshly collected urine should be used for analysis, immediate freezing prior to analysis at −85 °C is essential
[f]In general, enzymatic work-up as a first step is advised. In some cases (common mutation or small gene), mutation analysis as first step
[g]Liver biopsy is not routinely justified

Prenatal Diagnosis

Prenatal diagnosis is only relevant for SAHH, ADK, CBS, ETHE1, and SUOX deficiencies. Generally the first choice of method for each of these is mutation analysis in chorionic villous material provided that disease-causing mutations and their parental origin have been confirmed. Alternatively, enzyme assay in cultured amniocytes can be performed in some diseases.

DNA Testing

All genes in this chapter are known, and mutation analysis of genomic DNA isolated from peripheral blood, chorionic villi, amniocytes, or other cells is feasible. Sanger sequencing of individual genes or next-generation sequencing of gene panels are used. For mutations suspected to affect splicing, mRNA analysis in appropriate tissues may be necessary.

Treatment Summary

The general treatment goal for disorders of sulfur amino acid and hydrogen sulfide metabolism is correcting biochemical abnormalities in order to suppress their adverse effects. This causal treatment primarily consists in various combinations of high doses of cofactors, low-protein or low-methionine or low-cysteine diet, and supplementation of metabolites behind the enzymatic block. Betaine is an additional means to decrease homocysteine concentration.

In *MAT I/III deficiency*, methionine restriction is indicated in symptomatic patients and those with brain imaging changes. It is justified also in asymptomatic patients with severe deficiency and plasma methionine >500–800 μmol/L. AdoMet supplementation may be necessary. It seems that *GNMT deficiency*, *cystathionase deficiency*, and *autosomal dominant MATI/III deficiency* do not require treatment. In *AdoHcy hydrolase deficiency*, low-methionine diet can decrease plasma AdoMet and AdoHcy, with a positive effect on methylation and clinical and biochemical abnormalities (Barić et al. 2005). Phosphatidylcholine, creatine, and cysteine supplementation may be useful. Liver transplantation seemed beneficial in one patient with short follow-up. *CBS-deficient* patients are treated with varying doses of pyridoxine if responsive in the pyridoxine test. Folate and cobalamin should be added to avoid vitamin depletion and stimulate homocysteine remethylation. Betaine and/or a low-methionine diet (sometimes with methionine-free/cystine-enriched amino acid mixture) may also be needed in partial responders but necessary in pyridoxine nonresponsive patients. In *isolated sulfite oxidase deficiency*, partial success with low-protein diet combined with methionine- and cysteine-free amino acid mixture has been reported only in late-onset patients (Touati et al. 2000). Low methionine diet may ameliorate the liver phenotype in *adenosine kinase deficiency.* For *MATII deficiency and mercaptopyruvate sulfurtransferase deficiency*, no successful causal treatment has been reported. In *ethylmalonic encephalopathy*, metronidazole and *N*-acetylcysteine may reduce some symptoms. Early liver transplantation may be an option to reverse otherwise unfavorable outcome. In *MTO deficiency*, metronidazole can reduce methanethiol production by gut bacteria.

Emergency Treatment

Methionine Adenosyltransferase I/III Deficiency (AR and ADa forms)

If unexplained neurological signs are present with very high methionine level, discontinuance of methionine intake for 1–3 days followed by low-methionine diet until symptoms disappear, in combination with AdoMet supplementation (for instance, at a dose of 400 mg twice daily, Surtees et al.

1991), seems to be indicated. See also the comment [b] below the standard treatment table.

S-Adenosylhomocysteine Hydrolase Deficiency

Severe cases, such as those presenting with fetal hydrops, insufficiency of liver synthetic function, and severe muscular hypotonia leading to respiratory insufficiency, may potentially benefit from strict methionine restriction and choline and cysteine supplementation in combination with vigorous symptomatic treatment.

Ethylmalonic Encephalopathy

Continuous renal replacement therapy may help to reestablish metabolic control during acute metabolic decompensations in patients on chronic treatment with *N*-acetylcysteine and metronidazole (Kitzler et al. 2019).

For other disorders from this group, emergency situations amenable to specific disease-related emergency treatment are not likely. A diet low in protein and an amino acid mixture without cystine and methionine may be helpful in mild sulfite oxidase deficiency.

Standard Treatment

Disease	Comment	Medication/diet	Dosage[a]	Goals
22.1 MAT I/III deficiency	For the autosomal dominant form of the disease, treatment does not seem to be indicated For the autosomal recessive form, if plasma methionine concentrations are above risky level (clear risk above 800 µmol/L, existing risk above 500–600 µmol/L), a methionine-restricted diet is recommended If the mean plasma methionine is below 500–600 µmol/L, treatment does not seem to be indicated	Low-methionine diet	In infancy ~15–20 mg of methionine/kg/day; later less as expressed in mg/kg/day and according to clinical and biochemical parameters	Disappearance/prevention of clinical symptoms Normalization of brain imaging findings The aim of the diet is to maintain methionine levels around 500–600 µmol/L, even in asymptomatic individuals It should be borne in mind that lowering plasma methionine below 500 µmol/L in patients with some residual MAT I/III activity may further limit the flux through MAT I/III and further decrease the availability of AdoMet (Mudd et al. 2001)
	AdoMet supplementation, especially if methionine intake is limited, may be necessary	*S*-adenosylmethionine	2–3 × 400 mg daily per os[b]	Clinical improvement, normalization of plasma and/or CSF AdoMet; normalization of hyperhomocysteinemia
22.2 Methionine adenosyltransferase II deficiency	No causal treatment; surgery and other measures according to risk assessment of thoracic aorta aneurysm development			
22.3 GNMT deficiency	There is no evidence that therapy is necessary; low-methionine diet can correct biochemical abnormalities. It may be indicated when plasma methionine reaches values above 500–600 µmol/L, which may be risky regardless of cause	Low-methionine diet	In infancy ~15–20 mg of methionine/kg/day; later less as expressed in mg/kg/day and according to clinical and biochemical parameters	Correction of biochemical abnormalities and potential neurological problems due to high hypermethioninemia
22.4 AHCY deficiency	Due to small number of patients, these recommendations are based only on pathogenetic hypotheses and limited clinical experience Liver transplantation seemed beneficial in one patient with a short follow-up	Low-methionine diet	In infancy natural protein intake containing ~10–20 mg/kg/day of methionine, depending on the severity of the disease and biochemical findings, in combination with methionine-free amino acid mixture to meet needs for proteins	Clinical improvement and decrease of AdoMet and AdoHcy as close to normal values as possible, while avoiding protein malnutrition

Disease	Comment	Medication/diet	Dosage[a]	Goals
		Phosphatidylcholine	3 × 600–1200 mg/day	Avoidance of possible phosphatidylcholine and choline deficiency
		N-acetylcysteine	3 × 100–200 mg/day	Avoidance of possible glutathione deficiency
		Creatine (may be useful theoretically)	3–5 g/day	Avoidance of possible creatine deficiency
22.5 ADK deficiency	Low methionine diet should be considered as a therapeutic option, since it ameliorates the liver phenotype clinically and biochemically. Positive effect on the neurological outcome has only been reported in a single case. Diazoxide is recommended for recurrent hypoglycemia when it is due to hyperinsulinism (Barić et al. 2017)	Low methionine diet	Daily intake of 15–20 mg of methionine per kg of body weight in infants and small children; later less as expressed in mg/kg/day and according to clinical and biochemical parameters	Improvement of clinical and biochemical indices of liver disease
22.6 CBS deficiency[c]	*Test of pyridoxine responsiveness* should be done on normal protein intake at the beginning of the treatment (for details, see above) Before test possible folate and cobalamin deficiency should be corrected to assure proper assessment of the test results	A. Pyridoxine responders and partial responders		**Clinical targets:** For early diagnosed patients, prevention of all the complications of CBS deficiency while maintaining normal growth and nutrition For late-diagnosed patients, prevention of further complications, especially thromboembolic disease **Biochemical targets**: Maintenance of tHcy concentration as close to normal as possible. In fully responsive patients, standard doses can lead to tHcy levels below 50 µmol/L (and sometimes within the normal range in extreme responsive patients). Some patients who are partially responsive to pyridoxine may be able to achieve a tHcy level below 50 µmol/L if they are also on a low-Met diet; for others it is not a realistic goal. Excessive methionine restriction, with plasma methionine concentrations that are sometimes below the normal range, may impair growth and neurodevelopmental progress in children. In pyridoxine unresponsive patients, it is recommended to keep tHcy levels at least below 100 µmol/L, but this may need revision when very long-term data become available (Morris et al. 2017). Plasma methionine levels in patients treated with betaine should be kept below 800 µmol/L (it is probably safer below 500–600 µmol/L)
		Pyridoxine	The pyridoxine dose should be the lowest that achieves the biochemical targets. Recommended doses are up to 10 mg/kg/day divided into 1–3 doses; doses above 500 mg/day should be avoided	
		Folate[d]	Optimal dose is not known; up to 1 mg/day is probably sufficient if folate deficiency is not present	
		Hydroxocobalamin	Vitamin B_{12} should be monitored and supplemented if deficient	
		Low-methionine diet (for partially responsive patients only)	The degree of methionine or natural protein restriction required varies and is determined for each patient according to their plasma tHcy, methionine, and other parameters	
		Betaine (for partially responsive patients only)	Patients' responses to betaine are variable and optimal doses have to be individualized. For children, the initial betaine dose is 50 mg/kg twice daily. For adults, the starting dose is 3 g twice a day. The dose and frequency are adjusted according to response. There is unlikely to be any benefit in exceeding a dose of 150–200 mg/kg/day	

Disease	Comment	Medication/diet	Dosage[a]	Goals
	Guidelines for protein intake in methionine-restricted diet are very approximate. Diet must be adjusted, in combination with other measures, to achieve therapeutic goal, if possible, but should not jeopardize the patient; therefore strict monitoring of growth and nutritional indices (including aromatic and branched chain amino acids) is necessary	B. Pyridoxine nonresponders		
		There is no evidence that long-term pyridoxine is beneficial if there is no biochemical response in a properly conducted test (Morris et al. 2017)		
		Folate[d]	Optimal dose is not known; less than 1 mg/day is probably sufficient if folate deficiency is not present	
	In nearly all CBS-deficient patients, high remethylation activity may lead to folate and/or cobalamin depletion; therefore, folate and cobalamin should be added to the therapy	Cobalamin	Vitamin B_{12} should be monitored and supplemented if deficient	
		Low-methionine diet	Patients may require only isolated mild protein/methionine restriction or more severe restriction combined with amino acid mixture administration. The combined intake of low natural protein and methionine-free/cystine-enriched amino acid mixture (total protein equivalent) should follow the WHO/FAO recommendations (Joint FAO/WHO/UNU Expert Consultation on Protein and Amino Acid Requirements in Human Nutrition 2007). Methionine intake in natural protein depends on age and should be adjusted to maintain plasma tHcy levels <100 μmol/L while avoiding protein over-restriction. This can be typically achieved by prescribing 0.4–1.0 g natural protein/kg/day; however, higher or lower intake may be needed. If diet is based on calculation of methionine intake, appropriate amount may be between 4 and 10 mg/kg/day, with higher needs in infancy, particularly early infancy	
		Betaine	See pyridoxine responders	

Disease	Comment	Medication/diet	Dosage[a]	Goals
22.7 CTH deficiency	The disorder seems benign and therapy unnecessary			
22.8 Methanethiol oxidase deficiency	There is no standard treatment for this recently described disease, and options provided are based on pathogenesis (low methionine diet, metronidazole) and short trial in a single patient (metronidazole), respectively (Pol et al. 2018). Although an effect is expected from metronidazole, it is not recommended as prophylactic treatment	Metronidazole Low-protein/low methionine diet	Metronidazole: children 20–30 mg/kg/day three times daily; adults 400 mg three times daily (doses provided here are those usually used for anaerobic infections and for this indication may depend on the effect, occasion, and duration of the therapy/prophylaxis) Low-protein/low methionine diet can be considered but should not be over-restrictive so that methionine intake carefully adjusted to avoid harmful effects	To minimize the malodor while avoiding side effects
22.9 Isolated SUOX deficiency	The treatment has been useful only in milder forms of the disease. The diet must be carefully monitored to avoid protein malnutrition. Thiamine and pyridoxine can be added to avoid thiamine and pyridoxal-5-phosphate deficiency due to sulfite accumulation	Low-methionine and low-cysteine diet	Dependent on age and biochemical markers of the disease and protein status	Clinical improvement, decrease of toxic metabolites (*S*-sulfocysteine, thiosulfate), to limit excitotoxicity (dextromethorphan)
		Dextromethorphan (NMDA receptor antagonist)	Dextromethorphan: 12.5 mg/kg daily (dosage reported in patient with molybdenum cofactor deficiency; largely variable dosage has been reported in nonketotic hyperglycinemia)	
22.10 Ethylmalonic encephalopathy	Metronidazole and *N*-acetylcysteine may improve metabolic abnormalities (decrease H_2S accumulation and the sulfur atom from H_2S, respectively), reduce some symptoms, and slow disease progression	Metronidazole *N*-acetylcysteine	Metronidazole 25–50 mg/kg/day three times daily *N*-acetylcysteine 50–100 mg/kg/day in 2–3 doses	Decrease of H_2S accumulation and assimilation of the sulfur atom from H_2S, respectively, reducing some symptoms and slowing disease progression
22.11 Mercaptopyruvate sulfurtransferase deficiency	This condition could be benign	Not reported	–	–

[a]With the exception of CBS deficiency, given doses are arbitrary and frequently not evaluated in a sufficient number of patients for each given indication; therefore, they must be adjusted individually according to the diagnosis, patients' needs, and results of clinical and biochemical monitoring. A common problem is finding a proper balance between the wish to achieve desired therapeutic goals and avoidance of potentially serious side effects of higher doses than recommended/tested

[b]The dosage and route are only for approximate orientation. Information about AdoMet treatment in children is very limited. In adults daily doses from 50 mg to 3 g have been used. Intramuscular and intravenous forms of the drug do exist and should be considered in every patient individually

[c]Besides specific measures listed in table for CBS deficiency, other risk factors for thromboembolism should be checked and, if needed, treated. Dehydration and immobilization should be avoided to reduce the risk of thromboembolic disease. Patients who are poorly controlled or have had a vascular event may need additional treatment with anti-platelet drugs or anticoagulants. Surgery and anesthesia pose an additional risk of thrombosis. Biochemical control should be optimized before elective procedures. Standard anti-thrombotic measures such as elastic stockings, pneumatic leg compression systems, and early mobilization should be followed during and after surgery. Low molecular weight heparin is recommended in cases of prolonged immobilization. Nitrous oxide increases Hcy concentrations and should be avoided. Standard measures for preventing thrombosis are recommended for travel (Morris et al. 2017). Theoretically, phosphatidylcholine and creatine may inhibit transfer of methyl groups and thereby diminish the production of *S*-adenosylhomocysteine and homocysteine

[d]Folinate is probably generally a better option than folate, but folate should be satisfactory in most cases, except in those where parenteral use is necessary (folinate is available for parenteral use and folate is not)

Warning Boxes/Pitfalls

1. In patients treated with low-methionine diet, careful clinical and biochemical monitoring is necessary to avoid consequences of protein malnutrition.
2. Long-term folate therapy in high doses may be associated with increased cancer risk.
3. There is a high risk of peripheral neuropathy following long-term treatment with pyridoxine doses above 900 mg/day, but it has not been found in patients treated with less than 500 mg/day. In children, the safe dose is likely to depend on body weight; there are few data but last guidelines suggest using doses up to 10 mg/kg/day, with a maximum of 500 mg/day (Morris et al. 2017).
4. A major potential problem of betaine therapy in CBS deficiency and other disorders with both elevated tHcy and methionine is potential increase of methionine to the concentrations that may be toxic for the brain, leading to cerebral edema and other consequences of excessive hypermethioninemia described above.
5. Accidental inhalation of betaine in powder form can cause pulmonary problems.

Experimental Treatment

For *CBS deficiency,* molecular chaperones have been investigated in proof of principle studies, while enzyme replacement therapy is in phase I/II of a clinical trial.

For *ethylmalonic encephalopathy*, early liver transplantation may be an option to reverse otherwise poor outcome (Dionisi-Vici et al. 2016). Diet restricted in sulfur-containing amino acids may contribute to better outcome in patients detected by newborn screening, particularly if liver transplantation would be proven as an option. In some patients, improvement in some symptoms has been observed with ubiquinone and/or riboflavin.

Follow-Up and Monitoring

Recommendations given in the table are only approximate guidelines and should be adjusted individually according to age, severity of the disease, compliance, and other factors.

Disease	Clinical follow-up and monitoring	Biochemical follow-up and monitoring
22.1 MAT I/III deficiency	Both for untreated patients and those on therapy: any neurological sign or symptom should be considered as a possible sign of the disease and reason for further clinical (including brain imaging) and metabolic evaluation. Therefore, neurological and cognitive evaluation should be performed regularly in all patients with the risk of grossly elevated plasma methionine (clear risk above 800 μmol/L and existing risk above 500–600 μmol/L). In these patients neurological testing should take place about once every 2–3 months in infants and every 6–12 months later in life. If indicated, brain MRI should be performed (Chien et al. 2015). For patients on low-methionine diet, additionally, signs of protein malnutrition should be regularly looked for	In untreated patients without symptoms, checking of methionine, AdoMet, and total homocysteine (tHcy) is justified. The frequency depends on the severity of enzyme deficiency and mode of inheritance. The autosomal dominant form of MAT I/III deficiency is considered benign and does not require regular biochemical monitoring. In patients with the autosomal recessive form of the disease with severe enzyme deficiency and previous plasma methionine close to 500 μmol/L or more, or abnormal tHcy values, checking should be more frequent (i.e., in infancy every 3 months, later every 3–12 months and after significant changes in dietary methionine intake). In patients with the autosomal recessive form and mild enzyme deficiency, if highest plasma methionine values, which should be checked after normal and high protein intake, are not close to 500 μmol/L, only sporadic checking of plasma methionine is indicated, i.e., when symptoms attributable to MAT I/III deficiency appear. In patients on low-methionine diet, regular monitoring of protein status and plasma amino acids is indicated (in infancy at least every 3 months, later every 6–12 months and after significant changes in dietary methionine intake). In hyperhomocysteinemic patients in similar intervals, tHcy should be measured and thrombophilia screen should be performed at least once

Disease	Clinical follow-up and monitoring	Biochemical follow-up and monitoring
22.2 MAT II deficiency	In individuals with *MAT2* mutations, regular cardiac evaluation by ultrasound and if needed other methods to check for possible development of thoracic aorta dilatation are indicated	Not possible due to the lack of biochemical markers
22.3 GNMT deficiency	In GNMT-deficient patients tending to have very high plasma methionine levels which have been related to central nervous system complications (see MAT I/III deficiency above), regular neurological and cognitive testing is justified. [a]Yearly liver ultrasound seems justified	Due to possible hypermethioninemia-related problems, plasma methionine checking in regular intervals is recommended (in infancy every 3 months, if indicated even more frequently, later every 6–12 months or depending on previous values). Liver function tests, alpha-fetoprotein[a]
22.4 AHCY deficiency	Careful evaluation of all body systems, particularly of the nervous system and development, muscles, liver, and coagulation. In infancy every 1–3 months, if indicated even more frequently, later every 3–6 months. This includes imaging studies, particularly regular liver imaging	Careful biochemical monitoring is mandatory to control both disease development and treatment to avoid their complications. The following tests are indicated: protein status, amino acids, AdoMet, AdoHcy, liver function tests, creatine kinase, alpha-fetoprotein, coagulation tests, liver imaging, while others depend on the clinical situation. Follow-up intervals depend on age and clinical course. In infancy this could be every 1–3 months, if indicated even more frequently, later every 3–6 months
22.5 ADK deficiency	Careful clinical evaluation with regular follow-up visits depending on age and severity is recommended (intervals ranging from 1 month to 1 year), including regular monitoring of psychomotor development and neurological examination and regular liver imaging Since epilepsy is often present in ADK deficiency, regular electroencephalography is recommended. In one patient retinal dystrophy was diagnosed; thus ophthalmological examination on a regular basis should be considered. Because of an increased incidence of cardiac defects, echocardiography should be performed in all patients and followed up accordingly. Several patients presented with cholelithiasis; thus abdominal ultrasound should be performed in cases of unexplained pain (colic)	Assays of protein status, plasma amino acids, tHcy, AdoMet, AdoHcy, adenosine in urine and/or dried blood spot, serum aminotransferases, total and direct bilirubin, ammonia, blood glucose, uric acid, coagulation tests, and alpha-fetoprotein are relevant. Regular blood glucose profiles should be performed, depending on the presence and treatment of recurrent hypoglycemia. A full blood count should be included in the regular monitoring to check for megaloblastic anemia
22.6 CBS deficiency	The adequate frequency of monitoring depends on the severity of the disorder, treatment, compliance, age, status of the patient, and previous complications (e.g., thrombosis). Approximate schedule could be the following: Neurological and, depending on age, developmental or mental evaluation in infancy every 3 months, later every 6–12 months. Ophthalmology examination yearly. Bone mineral density once in 1–3 years. Vascular status every 6–12 months, depending on the severity of the disease and clinical course	Plasma amino acids and total homocysteine in infancy every 1–3 months, if indicated even more frequently, later every 3–6 months. If tHcy is monitored in dried blood spots, this test may be done more frequently. In patients on low-methionine diet protein status in the same intervals. Unless on supplementation, serum cobalamin and folate every 3–6 months. Thrombophilia screening should be considered once. Lipids first time at age 2–3 years, afterward, if normal, every 2–3 years, if not every 3 months alongside therapy
22.7 CTH deficiency	Not necessary	
22.8 MTO deficiency	Malodor can be monitored clinically. Possible related psychological burden may need psychologist's evaluation	If metronidazole is used, caution should be taken because of possible side effects. If low-protein/low methionine diet is used, protein status should be checked to avoid methionine deficiency and/or protein malnutrition
22.9 Isolated SUOX deficiency	General and, particularly, neurological (including EEG and imaging) and developmental evaluation in infancy every 1–3 months, later every 3–6 months, if indicated more frequently. Ophthalmology every 6 months, if indicated, more frequently	If on diet, protein status, amino acids, *S*-sulfocysteine, thiosulfate, sulfite in infancy every 1–3 months, if indicated more frequently, later every 3–6 months

Disease	Clinical follow-up and monitoring	Biochemical follow-up and monitoring
22.10 Ethylmalonic encephalopathy	General and, particularly, neurological (including EEG and imaging) and developmental evaluation in infancy every 1–3 months, later every 3–6 months, if indicated more frequently. Nutritional evaluation	Blood count according to blood losses in stool. Specific markers of the disease activity include lactate, plasma and urinary thiosulfate and sulfite, urinary ethylmalonate, and plasma C4- and C5-acylcarnitines. The frequency of monitoring depends on clinical condition and is more frequent in crises and/or following active treatment attempts, like liver transplantation. Otherwise it can be carried out in parallel with clinical evaluation, every 1–3 months in infancy, later every 3–6 months, if indicated more frequently
22.11 Mercaptopyruvate sulfurtransferase deficiency	If the disease is associated with intellectual disability, regular cognitive assessment seems justified	There is no evidence that intervention in this very rare disorder is needed or effective. Specific markers would be beta-mercaptolactate cysteine disulfide (urine), mercaptopyruvate, and mercaptolactate. It is questionable if this would have practical meaning

[a]In mice, in the long term significant liver disease may take place, including hepatocellular carcinoma; therefore, liver ultrasound and liver tumor markers checking may be justified

Online Resources

1. Bindu PS, Nagappa M, Bharath RD, Taly AB (2017) Isolated sulfite oxidase deficiency. GeneReviews® https://www.ncbi.nlm.nih.gov/books/NBK453433/ Sep21, 2017
2. Di Meo I, Lamperti C, Tiranti V (2017) Ethylmalonic encephalopathy. GeneReviews® https://www.ncbi.nlm.nih.gov/books/NBK453432/ Sep21, 2017.
3. Enzyme Commission numbers—http://www.chem.qmul.ac.uk/iubmb/enzyme/
4. Inborn Errors of Metabolism Knowledgebase (IEMbase)—http://www.iembase.org/
5. OMIM catalogue—http://www.ncbi.nlm.nih.gov/omim/
6. The Online Metabolic and Molecular Bases of Inherited Disease—https://ommbid.mhmedical.com/
7. Human Metabolome Database—http://www.hmdb.ca/

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