

10.1 Introduction

The sulfur amino acids are methionine, homocyst(e)ine, cystathionine, cyst(e)ine, and taurine. Defects in several of the enzymatic steps of their metabolism are known; some, but not all, result in human disease. The remethylation of homocysteine to methionine is closely dependent on folate and cobalamin cofactors, and relevant defects of their metabolism are therefore included in this chapter. Cystinuria and cystinosis, defects of renal tubular and lysosomal transport of cystine, respectively, are described in Chap. 13.

■ Clinical Features

The deficiencies of cystathionine β -synthase (CBS), sulfite oxidase, and methylenetetrahydrofolate reductase (MTHFR) may all result in central nervous system dysfunction, in particular mental retardation [1–3]. Defects of CBS and sulfite oxidase both cause dislocated lenses of the eyes, but the phenotypes are different otherwise. The manifestations of CBS deficiency, the most common of these disorders, and MTHFR deficiency range from severely affected to asymptomatic patients; both may cause vascular occlusion. Deficiency of sulfite oxidase is clinically uniform, but genetically heterogeneous, and functional deficiency of the enzyme can result from several inherited defects of molybdenum cofactor biosynthesis [2, 4]. Hereditary folate malabsorption and defects of cobalamin transport (transcobalamin II deficiency) or cobalamin cofactor biosynthesis (cblC-G diseases) may cause megaloblastic anemia, in addition to CNS dysfunction [3, 5, 6].

■ Biochemical Features

Homocystinuria and hyperhomocyst(e)inemia are biochemical denominators for deficiencies of CBS, MTHFR, cblC-G, and transcobalamin II, the major protein carrier of cobalamin in plasma [1, 3, 6]. Patients with the latter disorder or with inborn errors of cobalamin biosynthesis resulting in combined deficiency of both adenosylcobalamin and methylcobalamin also have

methylmalonic aciduria (cblC, cblD or cblF disease) [3]. CBS deficiency alone causes both homocystinuria and hypermethioninemia.

Mild hyperhomocysteinemia due to inadequate intake of folate and vitamin B₁₂ is associated with an increased risk of cardiovascular disease [7]. The number of persons at risk vastly exceeds the number of patients with inborn errors of metabolism, and public health policy recommendations for screening and intervention in patients with mild hyperhomocysteinemia await ongoing clinical trials.

■ Treatment

Treatment of CBS deficiency includes a low-methionine diet, vitamin B₆, folic acid, and betaine (N-trimethylglycine) [1]. Betaine works by (re)methylating homocysteine to methionine, and it is used in conjunction with folic acid in the treatment of MTHFR deficiency [3]. Hydroxycobalamin should be given to patients with methylmalonic aciduria; protein restriction, folic acid, vitamin B₆, betaine and other measures may also be appropriate, depending on which mutant class (cblA through cblG) a patient is assigned to by complementation analysis [3, 6].

Hereditary folate malabsorption and deficiency of transcobalamin II respond to intramuscular treatment with folinic acid and vitamin B₁₂, respectively [3].

Most cases of sulfite oxidase or molybdenum cofactor deficiency are fatal, but dietary restriction of protein and sulfur amino acids has brought clinical and biochemical improvement to patients with mild forms of the disease [2, 8].

■ Screening

Several countries carry out neonatal screening for CBS deficiency. The screening relies on the detection of hypermethioninemia, which is not always present at that age, and a significant proportion of patients may be missed. This may partly explain why the observed overall frequency is as low as 1:344 000 live births [1]. In some regions, the incidence of CBS deficiency is much higher, e.g., 1:65 000 in Ireland. Screening of Danish newborns for one prevalent mutation revealed a carrier frequency of 14:1000, corresponding to an incidence of homozygotes for this particular mutation of 1:20 500 [9]. For years or decades, severely increased plasma concentrations of homocyst(e)ine may go unnoticed in such patients until they present with a vascular catastrophe.

■ Prenatal Diagnosis

Except for isolated hypermethioninemia, which may be inherited as an autosomal dominant trait [10], inherited disorders of sulfur amino acids are autosomal recessive with a recurrence risk in subsequent sibs of 25%. Prenatal diagnosis is available to families in which the proband has been characterized by biochemical or molecular genetic analysis.

10.2 Nomenclature

No.	Disorder-affected component	Tissue distribution/ expression	Chromosomal localisation	MIM
10.1	Methionine adenosyl-transferase (MAT I/III)	Liver	10q22	250850
10.2	Cystathionine β -synthase (CBS)	Liver; lymphoblasts; cultured fibroblasts, amniocytes, and chorionic villi	21q22.3	236200
10.3	γ -Cystathionase (CTH)	Liver; lymphoblasts	16	219500
10.4	Sulfite oxidase (SUOX)	Liver; lymphoblasts; chorionic villi; cultured fibroblasts and amniocytes	12	272300
10.5	Molybdenum cofactor	Liver; lymphoblasts; chorionic villi; cultured fibroblasts and amniocytes		252150
10.5.1	type A (MOCS1)		6p21.3	603707
10.5.2	type B (MOCS2)		5q11	603708
10.5.3	type C, Gephyrin (GEPH)		14	603930
10.6	Methylenetetrahydrofolate reductase (MTHFR)	Liver; lymphocytes; lymphoblasts; chorionic villi; cultured fibroblasts	1p36.3	236250
10.7	Homocysteine methylation	Liver; cultured fibroblasts and amniocytes		
10.7.1	Methionine synthase (MS), cblG		1q43	250940
10.7.2	Methionine synthase reductase (MSR), cblE		5p15.2–p15.3	236270
10.8	Methylmalonyl CoA mutase (adenosylcobalamin) and methionine synthase (methylcobalamin)	Liver; cultured fibroblasts and amniocytes		
10.8.1	cblC			277400
10.8.2	cblD			277410
10.8.3	cblF			277380

No.	Disorder-affected component	Tissue distribution/ expression	Chromosomal localisation	MIM
10.9	Hereditary folate malabsorption	Intestine; choroid plexus		229050
10.10	Transcobalamin II (TC II)	Plasma	22q11.2-qter	275350

10.3 Metabolic Pathway

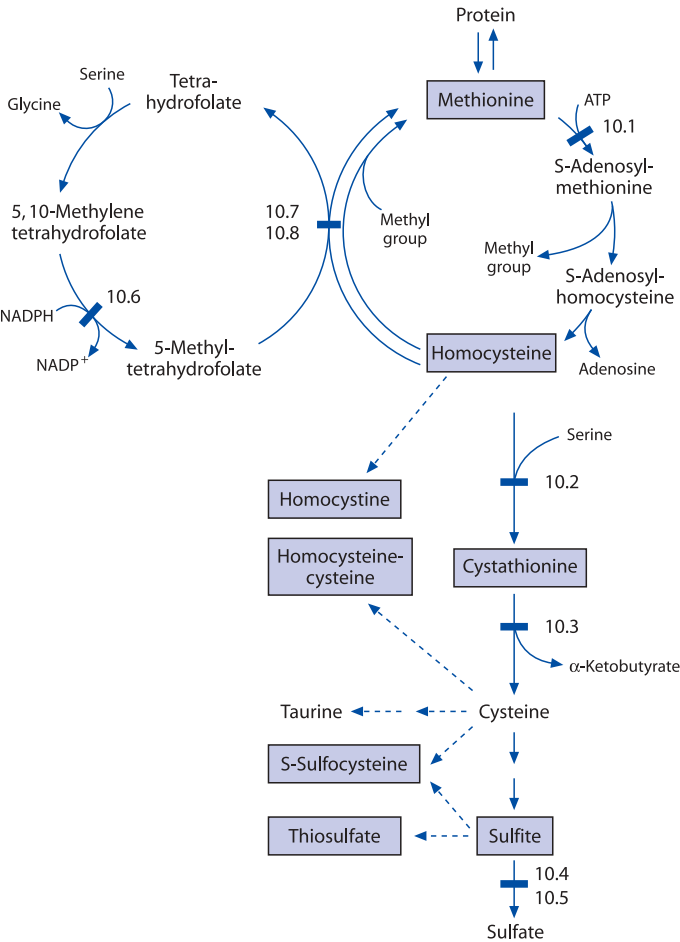


Fig. 10.1. Defects of transmethylation (methionine \rightarrow homocysteine), transsulfuration (methionine \rightarrow sulfate), and remethylation (homocysteine \rightarrow methionine) enzymes of sulfur amino acid metabolism: 10.1, methionine adenosyltransferase; 10.2, cystathionine β -synthase; 10.3, γ -cystathionase; 10.4, sulfite oxidase; 10.5, molybdenum cofactor; 10.6, methylenetetrahydrofolate reductase; 10.7 and 10.8, methionine synthase.

10.4 Signs and Symptoms

Table 10.1. Methionine adenosyltransferase deficiency (approx. 47 patients)

System	Symptoms/markers	Childhood	Adulthood
Characteristic clinical findings	Cabbage-like odor	±	
	Fetid breath		+
Special laboratory	Methionine (P)	↑	↑
	Methionine sulfoxide (P, U)	↑	↑
	Dimethylsulfide (breath)		↑
CNS	Demyelination	±	±
	Neurologic dysfunction	±	±

Table 10.2. Cystathionine β -synthase deficiency

System	Symptoms/markers	Childhood	Adulthood
Characteristic clinical findings	Ectopia lentis	±	±
	Mental retardation	±	±
	Thromboembolic episodes	±	±
	Osteoporosis	±	±
Special laboratory	Methionine (P)	↑	↑
	Homocyst(e)ine, free/total (P)	↑	↑
	Homocysteine-cysteine (P)	↑	↑
	Cyst(e)ine (P)	↓	↓
	Homocystine (U)	↑	↑
	Homocysteine-cysteine (U)	↑	↑
	Cyanide nitroprusside test (U)	+	+
CNS	Thromboses/infarcts	±	±
	Mental retardation	±	±
	Psychiatric symptoms	±	±
	Seizures	±	±
	Ectopia lentis	±	±
Eyes	Myopia	±	±
	Osteoporosis	±	±
Skeletal	Scoliosis	±	±
	Arachnodactyly – ‘marfanoid features’	±	±
	Sternal deformities	±	±
	Genu valgum	±	±
	Occlusions	±	±
Vascular	Occlusions	±	±
Dermatological	Malar flush	±	±

Table 10.3. γ -Cystathionase deficiency

System	Symptoms/markers	Childhood	Adulthood
Characteristic clinical findings	None		
Special laboratory	Cystathionine (P)	↑	↑
	Cystathionine (U)	↑	↑

Table 10.4. Sulfite oxidase deficiency (approx. 20 patients)

System	Symptoms/markers	Infancy	Childhood
Characteristic clinical findings	Seizures, therapy-resistant	+	+
	Ectopia lentis		+
	Psychomotor retardation		+
Special laboratory	Sulfite test (U)	+	+
	S-sulfocysteine (P)	↑	↑
	S-sulfocysteine (U)	↑	↑
	Taurine (P)	↑	↑
	Taurine (U)	↑	↑
	Sulfate (U)	↓	↓
	Cystine (P)	↓	↓
	Thiosulfate (U)	↑	↑
CNS	MRI/CT: brain atrophy, dilated ventricles		±
	Axial hypotonia/peripheral hypertonicity	+	
	Major motor seizures	+	+
	Developmental delay		+
	Hemiplegia, ataxia, choreiform movements		+
	Microcephaly		+
Eyes	Ectopia lentis		+
GI	Feeding difficulties	+	+
Other	Dysmorphic features	±	±
	Marfanoid features (in adolescence)		±

Table 10.5. Molybdenum cofactor deficiency (>80 patients)

System	Symptoms/markers	Infancy	Childhood
Characteristic clinical findings	Seizures, therapy-resistant	+	+
	Ectopia lentis		+
	Psychomotor retardation		+
Routine laboratory	Uric acid (P)	↓	↓
	Uric acid (U)	↓	↓
Special laboratory	Sulfite test (U)	+	+
	S-sulfocysteine (P)	↑	↑
	S-sulfocysteine (U)	↑	↑
	Taurine (P)	↑	↑
	Taurine (U)	↑	↑
	Sulfate (U)	↓	↓
	Cystine (P)	↓	↓
	Thiosulfate (U)	↑	↑
	Xanthine (U)	↑	↑
	Hypoxanthine (U)	↑	↑
CNS	MRI/CT: brain atrophy, dilated ventricles		±
	Axial hypotonia/peripheral hypertonicity	+	
	Major motor seizures	+	+
	Developmental delay		+
	Hemiplegia, ataxia, choreiform movements		+
Eyes	Ectopia lentis		+
GI	Feeding difficulties	+	+
Other	Dysmorphic features	±	±

Table 10.6. Methylene tetrahydrofolate reductase deficiency (approx. 50 patients)

System	Symptoms/markers	Childhood	Adulthood
Characteristic clinical findings	Mental retardation	±	±
Special laboratory	Methionine (P)	n-↓	n-↓
	Homocyst(e)ine, total (P)	↑	↑
	Homocysteine-cysteine (P)	↑	↑
	Cyanide nitroprusside test (U)	+	+
	Homocystine (U)	↑	↑
	Cystathionine (U)	n-↑	n-↑
	5-methyl-THF (CSF)	↓	↓
CNS	5HIAA/HVA (CSF)	↓	↓
	Microcephaly	±	±
	Mental retardation	±	±
	Gait disturbances	±	±
	Psychiatric disturbances		±
	Seizures	±	±
	Abnormal EEG	±	±
Vascular	Occlusions	±	±
Muscular	Limb weakness	±	±

Table 10.7.1. Methionine synthase deficiency (cblG) (approx. 20 patients)

System	Symptoms/markers	Childhood	Adulthood
Characteristic clinical findings	Developmental delay	+	+
	Megaloblastic anemia	+	+
Routine laboratory	Macrocytic anemia	+	+
	Abnormal EEG	±	±
	CT: cerebral atrophy	±	±
Special laboratory	Methionine (P)	↓-n	↓-n
	Homocyst(e)ine, free/total (P)	↑	↑
	Homocystine (U)	↑	↑
	Figlu (U)	n-↑	n-↑
CNS	Mental retardation	±	±
	Hypotonia	±	±
	Seizures	±	±
	Gait abnormalities	±	±
	Peripheral neuropathy	±	±
Eyes	Nystagmus	±	±
	Abnormal ERG	±	±
	Decreased vision	±	±

Table 10.7.2. Methionine synthase reductase deficiency (cblE) (approx. 12 patients)

System	Symptoms/markers	Childhood	Adulthood
Characteristic clinical findings	Developmental delay	+	+
	Megaloblastic anemia	+	+
Routine laboratory	Macrocytic anemia	+	+
	Abnormal EEG	±	±
	CT: cerebral atrophy	±	±
Special laboratory	Methionine (P)	↓-n	↓-n
	Homocyst(e)ine, free/total (P)	↑	↑
	Homocystine (U)	↑	↑
	Figlu (U)	n-↑	n-↑
CNS	Mental retardation	±	+
	Hypotonia	±	±
	Seizures	±	±
	Gait abnormalities	±	±
	Peripheral neuropathy	±	±
Eyes	Nystagmus	±	±
	Abnormal ERG	±	±
	Decreased vision	±	±

Table 10.8.1. Functional methylmalonyl CoA mutase and methionine synthase deficiency (cblC) (>100 patients)

System	Symptoms/markers	Infancy	Childhood	Adolescence
Characteristic clinical findings	Developmental delay	±	±	±
	Feeding difficulties/failure to thrive	±	±	±
	Macrocytic anemia	±	±	±
Routine laboratory	Macrocytic anemia	±	±	±
	Hypersegmented neutrophils	±	±	±
	Neutropenia	±	±	±
	Thrombocytopenia	±	±	±
	Acidosis	±	±	±
Special laboratory	Homocystine (U)	↑	↑	↑
	Methylmalonic acid (U)	↑	↑	↑
	Methionine (P)	↓-n	↓-n	↓-n
	Homocyst(e)ine, free/total (P)	↑	↑	↑
	Cystathionine (U)	n-↑	n-↑	n-↑
	Figlu (U)	n-↑	n-↑	n-↑
CNS	Microcephaly	±	±	±
	Hydrocephalus	±	±	±
	Hypotonia	±	±	±
	Extrapyramidal signs	±	±	±
	Seizures	±	±	±
	Myelopathy	±	±	±
	Dementia	±	±	±
	Psychosis	±	±	±
	Pigmentary retinopathy	±	±	±
	Decreased visual acuity		±	
Eyes	Nystagmus		±	
	Renal failure/hemolytic uremic syndrome	±	±	

Table 10.8.2. Functional methylmalonyl CoA mutase and methionine synthase deficiency (cblD) (2 patients)

System	Symptoms/markers	Adolescence
Characteristic clinical findings	Developmental delay	±
	Abnormal behavior	±
Special laboratory	Homocystine (U)	↑
	Methylmalonic acid (U)	↑
	Homocystine (P)	↑
	Methionine (P)	↓
	Cystathionine (P)	↑
CNS	Neuromuscular problems	±

Table 10.8.3. Functional methylmalonyl CoA mutase and methionine synthase deficiency (cblF) (6 patients)

System	Symptoms/markers	Infancy	Childhood
Characteristic clinical findings	Developmental delay	±	±
	Feeding difficulties/failure to thrive	±	±
Routine laboratory	Macrocytic anemia	±	±
	Macrocytic anemia	±	±
	Hypersegmented neutrophils	±	±
	Neutropenia	±	±
Special laboratory	Thrombocytopenia	±	±
	Homocystine (U)	↑	↑
	Methylmalonic acid (U)	↑	↑
	Methionine	↓-n	↓-n
	Cobalamins (S)		↓-n
CNS	Hypotonia	±	
	Seizures		±
	Confusion, disorientation		±
Other	Minor facial anomalies	±	
	Stomatitis	±	
	Pigmentary skin abnormality		±
	Arthritis		±

Table 10.9. Hereditary folate malabsorption (14 patients)

System	Symptoms/markers	Childhood
Characteristic clinical findings	Megaloblastic anemia	+
	Neurologic deterioration	+
Routine laboratory	Folates (S, CSF)	↓
	Pancytopenia	±
	Low immunoglobulins	±
Special laboratory	Intestinal folate absorption	↓
	CSF penetration of folate	↓
	Cobalamins (P)	n
	Homocysteine, total (P)	n
	Figlu (U)	n-↑
CNS	Basal ganglia calcifications	±
	Mental retardation	±
	Peripheral neuropathy	±
	Seizures	±
	Movement disorder	±
GI	Mouth ulcers	±
	Diarrhea	±
Other	Failure to thrive	±

Table 10.10. Transcobalamin II deficiency (approx. 40 patients)

System	Symptoms/markers	Childhood
Characteristic clinical findings	Pancytopenia with recurrent infections	+
Routine laboratory	Megaloblastic anemia	+
	Neutropenia	+
	Thrombocytopenia	+
Special laboratory	Low immunoglobulins	±
	Transcobalamin II (P)	↓↓↓
	Unsaturated vitamin B ₁₂ binding capacity (UBBC) (S)	↓
	Homocysteine, total (P)	n-↑
	Methylmalonic acid (U)	n-↑
	Homocystine (U)	n-↑
	Figlu (U)	n-↑
CNS	Developmental delay	±
Other	Failure to thrive	±

10.5 Reference Values

The biochemistry of thiol compounds is complex, and reference values vary somewhat according to the sex and age of the individuals studied and according to the method of analysis [1, 7]. In women plasma homocysteine decreases during pregnancy and increases after menopause.

Determination of *total* plasma homocysteine and cysteine is preferable due to instability of free thiols in the presence of plasma proteins, which bind ~70% and ~30% of homocysteine and cysteine, respectively. The total amount of one of these compounds is the sum of the free thiol plus the residues bound via disulfide bonds to thiols, peptides, or proteins.

Test	Value	Unit
Cobalamins (S)	>200	pmol/l
Cystathionine (P, S)	<1	μmol/l
Cystathionine (U)	0.1–3 ^a	mmol/mol creat
Cysteine, free (P)	100–125	μmol/l
Cysteine, total (P)	174–378	μmol/l
Cysteine (U)	16–66	mmol/mol creat
Folates (erythrocyte)	>0.42	μmol/l
Folates (S)	4–20	nmol/l
Folates (CSF)	1.5–2×serum value	
Homocysteine, free (P)	1–5	μmol/l
Homocysteine, total (P)	5–15	μmol/l
Homocysteine (U)	3–10	μmol/day
	0.2–4	mmol/mol creat

Test	Value	Unit
Homocysteine-cysteine, free (P)	1–4	μmol/l
Homocysteine-cysteine (U)	<1	mmol/mol creat
Homocystine, free (P)	<1	μmol/l
Homocystine (U)	<1	mmol/mol creat
Hypoxanthine (U)	0.02–0.04	mmol/day
Methionine (P, S)	5–35	μmol/l
Methionine (U)	0.2–2	mmol/mol creat
Methylmalonic acid (U)	<20	mmol/mol creat
5-Methyl-THF (CSF)	41–182 (age-dependent)	nmol/l
S-Sulfocysteine (P, S)	<1	μmol/l
Taurine (P, S)	30–109	μmol/l
Taurine (U)	<1200 (<12 y) <2500 (>12 y)	μmol/day
	5–7	mmol/mol creat
Thiosulfate (U)	10	mmol/mol creat
Transcobalamin II (S)	800–1500	pg/ml
Unsaturated vitamin B ₁₂	1000–2000	pg/ml
binding capacity (UBBC) (S)		
Xanthine (U)	0.02–0.04	mmol/day

^a Higher in premature infants, certain tumors, thyreotoxicosis, and vitamin B₆ deficiency.

10.6 Pathologic Values/Differential Diagnoses

No.	Disorder	Methionine (P)	Total homo-cysteine (P)	Homo-cystine (U)	Cystathionine (U)	Sulfite (U)	Methylmalonic acid (U)	Xanthine/hypoxanthine (U)
10.1	MAT deficiency	50–2500	N	0	N	0	N	N
10.2	CBS deficiency	N–2000	↑↑↑	↑↑↑	↓–n	0	N	N
10.3	CTH deficiency	N	N	0	↑↑↑ 1000–5800 μmol/24 h	0	N	N
10.4	Sulfite oxidase deficiency	N	N	0	N	↑	N	N
10.5	Molybdenum cofactor deficiency	N	N	0	N	↑	N	↑
10.6	MTHFR deficiency	↓–n	↑↑	↑↑	n–↑	0	N	N
10.7	cblE and cblG diseases	↓–n	↑	↑	N	0	N	N
10.8	cblC, cblD, and cblF diseases	↓–n	↑	↑	N or	0	3.8–6416 mmol/mol creat (cblC)	N
10.9	Hereditary folate malabsorption	n–↓	N	0	N	0	N	N
10.10	Transcobalamin II deficiency	N	n–↑	0–↑	N	0	N–↑ 126–904 mmol/mol creat	N

Plasma levels are in μmol/l. N, normal.

10.7 Loading Test

A number of conditions outside the scope of this chapter are associated with mild hyperhomocysteinemia, including premature vascular disease and deficiencies of folate and vitamin B12 [7]. Oral methionine loading (0.1 g/kg) may be used to investigate such patients. Postloading plasma homocysteine levels reach a peak at 4–8 h and approach preloading values within 2–4 days. Together with plasma methionine, the baseline level and postloading rise of plasma homocysteine may provide information on the various inherited and acquired defects of homocysteine metabolism.

10.8 Diagnostic Flow Chart

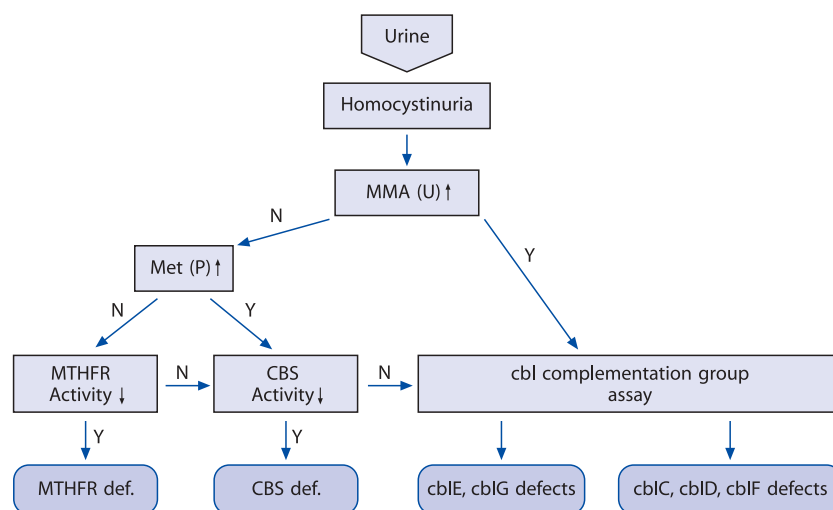


Fig. 10.2. Diagnostic flow chart for the patient with homocystinuria. Determinations of the level of methylmalonic acid (MMA) and methionine (Met) in urine and plasma, respectively, are the essential first steps. The biochemical diagnosis rests upon the appropriate enzyme assay or complementation group analysis in cultured fibroblasts. Y, yes; N, no.

10.9 Specimen Collection

Test	Precon- ditions	Material	Handling	Pitfalls
Cyanide nitroprus- side (U)		Random urine		Detection of other disulfides
Cystathionine (U)		Random urine	Freeze	Bacterial contamination: cystathionine → homo- cysteine (false negative)
Homocystine, free (P)		Plasma	Deproteinize immediately ^a	Protein-binding of thiol compounds at high tem- perature and storage
Homocysteine, total (P)		Plasma	Centrifuge and separate plas- ma within 2 h Liberate thiols before analy- sis	Continued production of homocysteine during storage of whole blood
Homocystine (U)		Random urine	Freeze	
Methionine (P, S)	Free diet, fasting	Plasma/ serum		
Sulfite (U)		Random urine	Analyze immediately	Autooxidation: sulfite → sul- fate by autooxidation (false negative) Drug interaction: patients taking 2-mercaptoethane- sulfonate (Mistabron) (false positive) Test strip out of date

^a Place blood sample on ice; prepare and deproteinize plasma within 30 min.

10.10 Prenatal Diagnosis

No.	Disorder	Material	Timing, trimester
10.2	CBS deficiency	Chorionic villi, cultured amniotic cells	I, II
10.4	Sulfite oxidase deficiency	Chorionic villi, amniotic fluid, cultured amniocytes	I, II
10.5	Molybdenum cofactor deficiency	Chorionic villi, amniotic fluid, cultured amniocytes	I, II
10.6	MTHFR deficiency	Chorionic villi, cultured amniocytes	I, II
10.7.2	cblE disease	Chorionic villi, cultured amniocytes	I, II
10.8	cblC and cblF diseases	Chorionic villi, cultured amniocytes, amniotic fluid	I, II
10.10	Transcobalamin II	Cultured amniocytes	II

Prenatal diagnosis of 10.1, 10.3, and 10.9 has not been reported.

10.11 DNA Analysis

No.	Disorder	Tissue	Methods
10.1	Methionine adenosyltransferase (MAT I/III) deficiency	Leukocytes	PCR SSCP Sequencing Minigene construction
10.2	Cystathionine β -synthase (CBS) deficiency	Whole blood impregnated on filter paper Leukocytes EBV-transformed lymphoblasts Cultured fibroblasts	PCR SSCP RNA extraction Reverse transcription Sequencing
10.4	Sulfite oxidase (SUOX) deficiency	Leukocytes Cultured fibroblasts	RNA extraction Reverse transcription PCR Sequencing
10.5	Molybdenum cofactor deficiency Type A (MOC S1) Type B (MOC S2) Type C, gephyrin (GEPH) deficiency	Leukocytes Cultured fibroblasts	RNA extraction Reverse transcription PCR Sequencing
10.6	Methylenetetrahydrofolate reductase (MTHFR) deficiency	Leukocytes Cultured fibroblasts	PCR SSCP RNA extraction Reverse transcription Sequencing
10.7	Methionine synthase (MS) deficiency, cblG Methionine synthase reductase (MSR) deficiency, cblE	Leukocytes Cultured fibroblasts	PCR SSCP Reverse transcription Sequencing
10.10	Transcobalamin II (TC II) deficiency	Leukocytes Cultured fibroblasts	Southern blotting Reverse transcription PCR Sequencing

DNA analysis of 10.3, 10.8 and 10.9 has not been reported.

10.12 Initial Treatment

■ Disorder 10.1: MAT Deficiency

Management, if required, may include dietary methionine restriction and/or administration of adenosylmethionine [1].

■ Disorder 10.2: CBS Deficiency

Patients diagnosed by neonatal screening should be placed on a low-methionine diet. Methionine restriction may not be acceptable to many patients diagnosed after infancy. While awaiting confirmation of the diagnosis by enzyme assay or DNA analysis, such patients can be given pharmacological doses of vitamin B₆ to test for biochemical responsiveness to this cofactor [1].

■ Disorder 10.3: CTH Deficiency

No therapy is required.

■ Disorder 10.4: Sulfite Oxidase Deficiency

Restriction of protein and sulfur amino acids may benefit patients with mild phenotype or late onset of disease [2, 8].

■ Disorder 10.5: Molybdenum Cofactor Deficiency

No therapy is currently available [2].

■ Disorder 10.6: MTHFR Deficiency

Initial management includes folic acid and betaine. Methionine, pyridoxine, cobalamin, and carnitine may also be of benefit [3].

■ Disorder 10.7: cblE and cblG Diseases

Patients with cblE and cblG disease respond to intramuscular hydroxycobalamin [3]. Folic acid and betaine have also been used.

■ Disorder 10.8: cblC, cblD, and cblF Diseases

Patients should be started immediately on intramuscular hydroxycobalamin [3]. Adjunctive therapy with protein restriction, betaine, folic acid, pyridoxine and possibly carnitine should be tried.

■ Disorder 10.9: Hereditary Folate Malabsorption

Some patients respond clinically and biochemically to large doses of oral folic or folinic acid. Parenteral therapy may be required. It is essential to document improvement of CSF folate level [5].

■ Disorder 10.10: Transcobalamin II Deficiency

Intramuscular vitamin B₁₂ is recommended [3]. Some patients also have received folic acid orally.

10.13 Summary

Most inborn errors of sulfur amino acid metabolism are easy to ascertain by metabolic screening of urine and measurement of plasma amino acids, including total homocysteine. Patients with severely increased plasma total homocysteine due to CBS deficiency, the most common of these disorders, may go undetected for years; early diagnosis and treatment are essential for a good outcome. Therapeutic efforts in some of the other disorders are restricted by our knowledge of pathophysiologic mechanisms. Even if therapy is not feasible or comes too late, a precise diagnosis may allow for prenatal testing in subsequent pregnancies. DNA analysis has to some extent replaced enzyme assay for diagnostic confirmation, but large numbers of allelic mutations may cause difficulties. Biochemical analysis remains crucial for the diagnosis and differential diagnosis of inborn errors of sulfur amino acids.

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