# Disorders of Glutathione and γ-Glutamyl Cycle

# 42

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## Contents




Summary

The γ-glutamyl cycle, comprising six enzymes, harbors four hereditary defects: γ-glutamylcysteine synthetase, glutathione synthetase, γ-glutamyl transpeptidase, and 5-oxoprolinase. Defects have also been identified in γ-glutamyltranspeptidase and dipeptidase (cysteinylglycinase); these conditions affect the biosynthesis of leukotrienes and will be discussed in Chap. 38.

Deficiency of either of the two synthetases results in decreased levels of glutathione and thus increased sensitivity to oxidative stress that results in hemolytic anemia. Glutathione synthetase deficiency occurs with different severity; the mild form is only associated with hemolytic anemia, whereas moderate and severe glutathione synthetase deficiency is associated also with metabolic acidosis, progressive neurological symptoms, and recurrent bacterial infections. 5-Oxoproline (pyroglutamic acid) is overproduced in glutathione synthetase deficiency due to lack of feedback inhibition. Treatment involves acidosis correction; administration of vitamin E, vitamin C, and N-acetylcysteine; and avoidance of drugs inducing hemolysis. γ-Glutamyl transpeptidase deficiency is associated with glutathionuria, cysteinylglycinase deficiency with cystinylglycinuria, and 5-oxoprolinase deficiency with 5-oxoprolinuria.


## 42.1 Introduction

Glutathione, which is produced and broken down in the γ-glutamyl cycle, participates in free radical scavenging, defense against oxidative stress, redox reactions, formation of deoxyribonucleotides, xenobiotics metabolism, and amino acid transport. Patients with genetic defects in four of the six γ-glutamyl cycle enzymes have been reported and they are all inherited as autosomal recessive traits (Larsson and Anderson 2001).

The biosynthesis of the tripeptide glutathione (γ-glutamyl cysteinylglycine) is catalyzed by γ-glutamylcysteine synthetase and glutathione synthetase. The initial degradative step is


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catalyzed by γ-glutamyl transpeptidase, which transfers the γ-glutamyl group to an acceptor, for example, an amino acid, to form γ-glutamyl amino acids. The latter are typically substrates of γ-glutamyl cyclotransferase which catalyzes release of the γ-glutamyl residue as 5-oxoproline (pyroglutamic acid) which is converted back to glutamate by 5-oxoprolinase. Glutathione acts as a feedback inhibitor of γ-glutamylcysteine synthetase.

γ–Glutamylcysteine synthetase deficiency has been described in more than ten patients in more than six families. All had hemolytic anemia, and in addition, two siblings also had cerebellar involvement, neuropathy, myopathy, and aminoaciduria. Glutathione synthetase deficiency has been reported in more than 50 patients in more than 40 families. According to clinical symptoms, glutathione synthetase deficiency can be classified as mild, moderate, or severe (Beutler et al. 1999). Patients with mild glutathione synthetase deficiency show hemolytic anemia as their only clinical symptom. Patients with moderate glutathione synthetase deficiency usually present in the neonatal period with metabolic acidosis, 5-oxoprolinuria, and hemolytic anemia. Patients with severe glutathione synthetase deficiency also develop progressive neurological symptoms (e.g., mental retardation, seizures, spasticity) and may also develop recurrent bacterial infections, due to defective granulocyte function. Several patients have died in early life due to acidosis and electrolyte imbalance. The acidosis is due to the overproduction of 5-oxoproline as a consequence of defective feedback regulation of the early steps of the γ-glutamyl cycle. As a consequence, accumulating γ-glutamylcysteine will be cleaved by γ-glutamylcyclotransferase and the amount of its product 5-oxoproline then surpasses the capacity of 5-oxoprolinase. Patients with moderate and severe glutathione synthetase deficiency usually excrete gram quantities of 5-oxoproline in urine. Patients with mild glutathione synthetase deficiency maintain cellular levels of glutathione which usually, but not always, is sufficient to prevent accumulation of 5-oxoproline in body fluids. Treatment of patients with glutathione synthetase deficiency includes acidosis correction and supplementation with the antioxidants vitamin E, vitamin C, and N-acetylcysteine, as well as avoidance of drugs known to precipitate hemolytic crises in patients with glucose-6-phosphate dehydrogenase deficiency.

Deficiency of γ-glutamylcysteine synthetase or glutathione synthetase results in low intracellular levels of glutathione. This can be demonstrated in erythrocytes, leukocytes, and cultured fibroblasts. Increased 5-oxoproline can only be determined via analysis of organic acids by gas chromatography–mass spectrometry (GC-MS). Analysis of the γ-glutamyl cycle enzymes in erythrocytes or nucleated cells is required for the diagnosis. The human genes for γ-glutamylcysteine synthetase and glutathione synthetase have been mapped and cloned and mutations in the genes have been characterized (Larsson and Anderson 2001; Ristoff et al. 2000, 2001; Njalsson et al. 2000).

γ-Glutamyl transpeptidase deficiency has been identified in five patients who excrete glutathione in their urine and have elevated plasma glutathione. Three of the five patients have CNS symptoms. Increased levels of urinary glutathione can be demonstrated by various chromatographic techniques. The human γ-glutamyl transpeptidase gene is a multigenetic family with several of its loci located on chromosome 22 (Larsson and Anderson 2001).

A tentative deficiency of cysteinylglycinase has been found in one patient with distinct neurological abnormalities. Its chromosomal location is 16q24.3. See also Chap. 38 for the latter two defects.

5-Oxoprolinase deficiency has been identified in eight patients who lack a consistent clinical syndrome. Urinary excretion of 5-oxoproline is elevated but less than in glutathione synthetase deficiency. Erythrocytes contain an incomplete γ-glutamyl cycle; they lack both γ-glutamyl transpeptidase and 5-oxoprolinase (Almaghlouth et al. 2012).

## 42.2 Nomenclature

| No. | Disorder | Alternative name | Abbreviation | Gene symbol | Chromosomal localization | Affected protein | OMIM no. | Subtype |
|---|---|---|---|---|---|---|---|---|
| **42.1** | Glutathionuria | Gamma-glutamyl transpeptidase deficiency | GGT1 | *GGT1* | 22q11.1-q11.2 | Gamma-glutamyl transpeptidase | 231950 | All forms |
| **42.2** | Oxoprolinuria | 5-Oxoprolinase deficiency | | | | 5-Ooxoprolinase | 260005 | All forms |
| **42.3** | Gamma-glutamylcysteine synthetase deficiency | Hemolytic anemia due to GGCS deficiency | GGCS | *GCLC* | 6p12 | Gamma-glutamylcysteine synthetase | 230450 | All forms |
| **42.4.1** | Glutathione synthetase deficiency, mild | 5-Oxoprolinuria | | *GSS* | 20q11.2 | Glutathione synthetase | 266130 | Mild form |
| **42.4.2** | Glutathione synthetase deficiency, severe | 5-Oxoprolinuria | | *GSS* | 20q11.2 | Glutathione synthetase | 266130 | Severe |

## 42.3 Metabolic Pathway

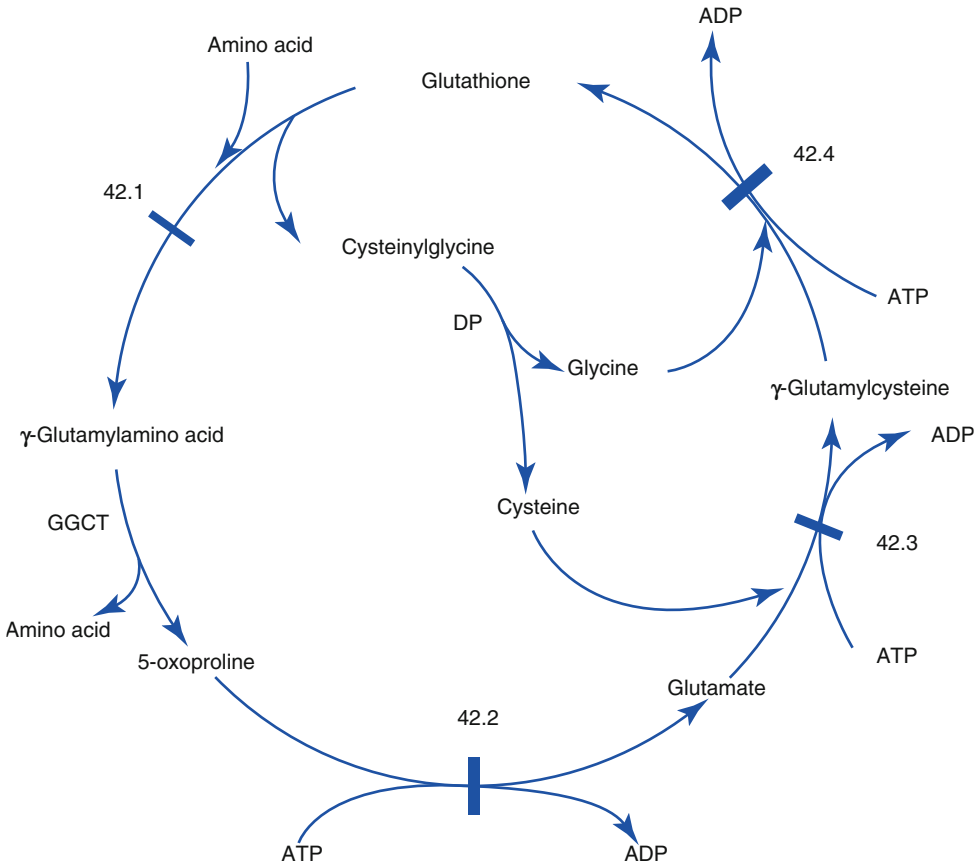


**Fig. 42.1** The γ-glutamyl cycle for the biosynthesis and degradation of glutathione including known metabolic defects: **42.1** γ-glutamyl transpeptidase, **42.2** 5-oxoprolinase, **42.3** γ -glutamylcysteine synthetase, **42.4** glutathione synthetase. *DP* dipeptidase (cysteinylglycinase), *GGCT* γ-glutamyl cyclotransferase. Metabolites that show pathological levels in the various enzymatic defects are marked in *bold*. Note the role of excess 5-oxoproline (pyroglutamic acid) as a marker for two of the four disorders

## 42.4 Signs and Symptoms

**Table 42.1** Glutathionuria

| System | Symptom | Neonatal | Infancy | Childhood | Adolescence | Adulthood |
|---|---|---|---|---|---|---|
| CNS | Mental retardation | | | ± | ± | ± |
| | Psychosis | | | ± | ± | ± |
| Other | **No consistent clinical picture** | | | | | |
| Special laboratory | Gamma-glutamyltranspeptidase (WBC,FB) | ↓ | ↓ | ↓ | ↓ | ↓ |
| | Glutathione (P) | ↑ | ↑ | ↑ | ↑ | ↑ |
| | Glutathione (RBC) | n | n | n | n | n |
| | Glutathione (U) | ↑ | ↑ | ↑ | ↑ | ↑ |

**Table 42.2** Oxoprolinuria

| System | Symptom | Neonatal | Infancy | Childhood | Adolescence | Adulthood |
|---|---|---|---|---|---|---|
| CNS | Retardation, psychomotor | ± | ± | ± | ± | ± |
| Digestive | Colitis | | | | ± | ± |
| | Diarrhea | | | | ± | ± |
| Musculoskeletal | Microcephaly | | ± | ± | | |
| Renal | Renal colic | | | ± | ± | ± |
| | Urolithiasis | | | ± | ± | ± |
| Othert | **No consistent clinical picture** | | | | | |
| Special laboratory | 5-Oxoprolien (U) | ↑ | ↑ | ↑ | ↑ | ↑ |
| | 5-Oxoprolinase (WBC, FB) | ↓ | ↓ | ↓ | ↓ | ↓ |
| Routine laboratory | Acidosis (B) | n | n | n | n | n |

**Table 42.3** Gamma-glutamylcysteine synthetase deficiency

| System | Symptom | Neonatal | Infancy | Childhood | Adolescence | Adulthood |
|---|---|---|---|---|---|---|
| CNS | Ataxia | ± | ± | ± | ± | ± |
| | Neuropathy | ± | ± | ± | ± | ± |
| | Psychosis | ± | ± | ± | ± | ± |
| Digestive | **Jaundice** | ± | ± | ± | ± | ± |
| Hematological | Anemia, hemolytic | + | + | + | + | + |
| | **Hemolytic anemia** | + | + | + | + | + |
| Musculoskeletal | Myopathy | ± | ± | ± | ± | ± |
| Routine laboratory | Hemoglobin (B) | ↓ | ↓ | ↓ | ↓ | ↓ |
| | Reticulocytes (B) | ↑ | ↑ | ↑ | ↑ | ↑ |
| Special laboratory | Amino acids, all | ± | ± | ± | ± | ± |
| | Gamma-glutamylcysteine synthetase (RBC,FB) | ↓↓↓ | ↓↓↓ | ↓↓↓ | ↓↓↓ | ↓↓↓ |
| | Glutathione (RBC) | ↓↓↓ | ↓↓↓ | ↓↓↓ | ↓↓↓ | ↓↓↓ |

**Table 42.4.1** Glutathione synthetase deficiency, mild

| System | Symptom | Neonatal | Infancy | Childhood | Adolescence | Adulthood |
|---|---|---|---|---|---|---|
| Digestive | Jaundice | ± | ± | ± | ± | ± |
| Hematological | Anemia, hemolytic | + | + | + | + | + |
| | **Hemolytic anemia** | + | + | + | + | + |
| Routine laboratory | Hemoglobin (B) | ↓ | ↓ | ↓ | ↓ | ↓ |
| | Reticulocytes (B) | ↑ | ↑ | ↑ | ↑ | ↑ |
| Special laboratory | 5-Oxoproline (U) | n-↑ | n-↑ | n-↑ | n-↑ | n-↑ |
| | Gamma-glutathione synthetase (RBC,FB) | ↓↓↓ | ↓↓↓ | ↓↓↓ | ↓↓↓ | ↓↓↓ |
| | Glutathione (RBC) | ↓↓ | ↓↓ | ↓↓ | ↓↓ | ↓↓ |

**Table 42.4.2** Glutathione synthetase deficiency, severe

| System | Symptom | Neonatal | Infancy | Childhood | Adolescence | Adulthood |
|---|---|---|---|---|---|---|
| CNS | Ataxia | | ± | ± | ± | ± |
| | Hypertonia | ± | ± | ± | ± | ± |
| | Hypotonia | ± | ± | ± | ± | ± |
| | **Neurological symptoms** | ± | ± | ± | ± | ± |
| | Retardation, psychomotor | ± | ± | ± | ± | ± |
| | Seizures | ± | ± | ± | ± | ± |
| Digestive | Jaundice | ± | ± | ± | ± | ± |
| Eye | Adaptation, dark impaired | | | ± | ± | ± |
| | Corneal clouding | | | ± | ± | ± |
| | Pigmentary retinopathy | | | ± | ± | ± |
| Hematological | **Hemolytic anemia** | + | + | + | + | + |
| Musculoskeletal | Myopathy | ± | ± | ± | ± | ± |
| Other | Recurrent bacterial infections | ± | ± | ± | ± | ± |
| | **Recurrent bacterial infections** | ± | ± | ± | ± | ± |
| Routine laboratory | Hemoglobin (B) | ↓ | ↓ | ↓ | ↓ | ↓ |
| | Lactic acidosis | + | + | + | + | + |
| | **Metabolic acidosis** | + | + | + | + | + |
| | Reticulocytes (B) | ↑ | ↑ | ↑ | ↑ | ↑ |
| Special laboratory | 5-Oxoproline (U) | ↑↑↑ | ↑↑↑ | ↑↑↑ | ↑↑↑ | ↑↑↑ |
| | Gamma-glutathione synthetase (RBC,FB) | ↓↓↓ | ↓↓↓ | ↓↓↓ | ↓↓↓ | ↓↓↓ |
| | Glutathione (RBC) | ↓↓ | ↓↓ | ↓↓ | ↓↓ | ↓↓ |

## 42.5 Reference Values

| Metabolite | |
|---|---|
| 5-Oxoproline (U) | <10 mmol/mol creat |
| Glutathione (RBC) | 4.6–10.9 nmol/mg Hb |

## 42.6 Pathological Values

| | Glutathione | | | 5-Oxo-proline | Acid–base balance | Reticulocytes | Hemolytic anemia |
|---|---|---|---|---|---|---|---|
| | (RBC) (B) | (U) | (P) | (U) | (B) | (B) | (B) |
| **42.1** Glutathionuria | N | ↑ | ↑ | N | N | N | N |
| **42.2** Oxoprolinuria | N | N | N | ↑ | N | N | N |
| **42.3** γ Glutamylcysteine synthetase deficiency | ↓↓ | N | – | N | N | ↑ | ↑ |
| **42.4.1** Glutathione synthetase deficiency, mild | ↓↓ | N | – | N-↑ | N | ↑ | ↑ |
| **42.4.2** Glutathione synthetase deficiency, severe | ↓↓ | N | – | ↑↑↑ | Acidosis | ↑ | ↑ |

## 42.7 Diagnostic Flow Chart

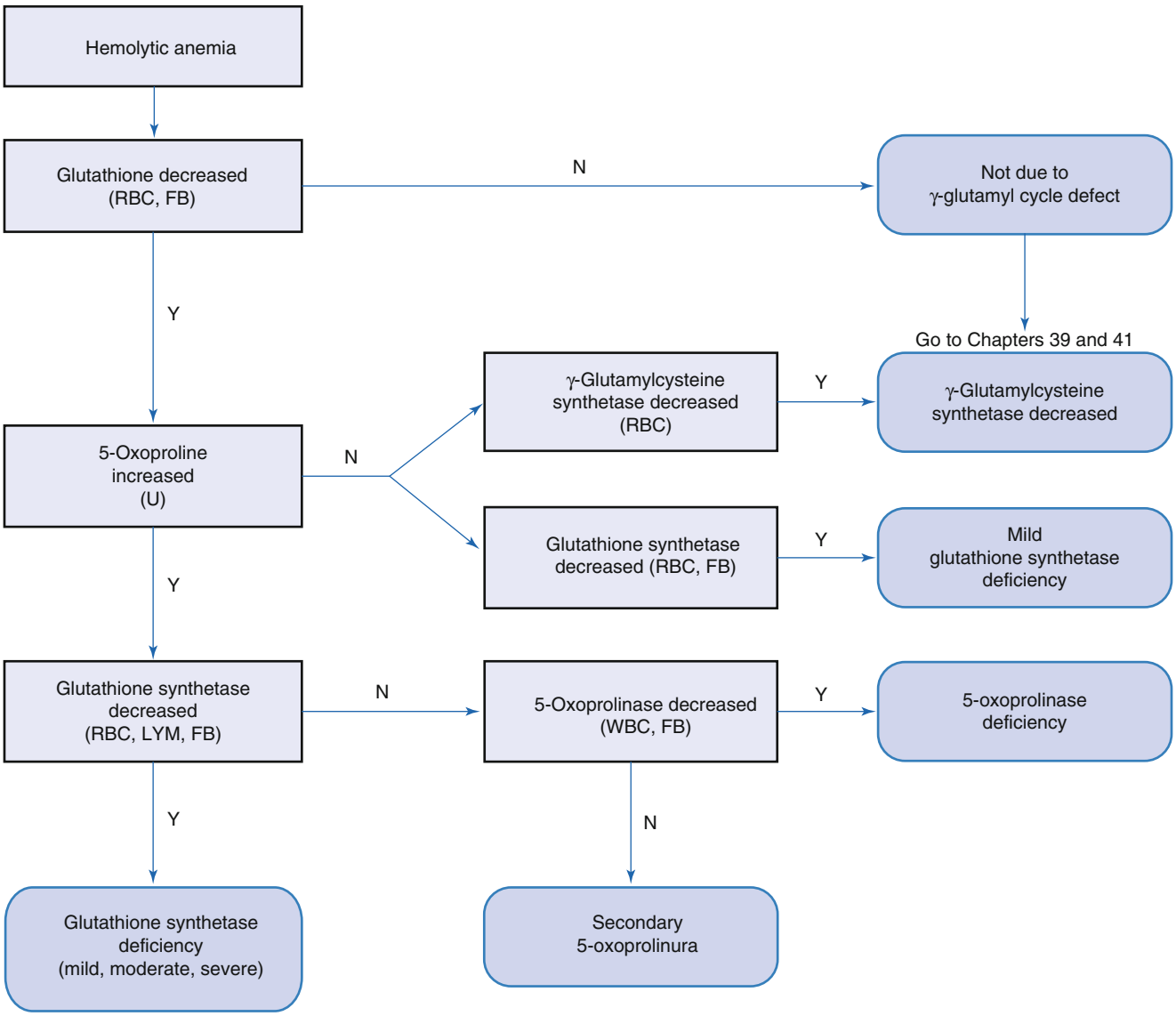


**Fig. 42.2** Diagnostic flow chart for disorders of the γ-glutamyl cycle presenting with hemolytic anemia

## 42.8 Specimen Collection

| Test | Preconditions | Material | Handling | Pitfalls |
|---|---|---|---|---|
| Glutathione | – | RBC, B, FB | Frozen (–20 °C) | Assays that do not detect oxidized glutathione tend to underestimate glutathione in stored samples |
| γ-Glutamylcysteine synthetase | – | RBC, LYM, FB | Frozen (–20 °C) | |
| Glutathione synthetase | – | RBC, LYM, FB | Frozen (–20 °C) | |
| γ-Glutamyl transpeptidase | – | RBC, FB, P | Frozen (–20 °C) | |
| γ-Glutamyl cyclotransferase | – | RBC, LYM, FB | Frozen (–20 °C) | |
| 5-Oxoprolinase | – | WBC, FB | Frozen (–20 °C) | |

| Test | Preconditions | Material | Handling | Pitfalls |
|---|---|---|---|---|
| 5-Oxoproline | – | U | Frozen (−20 °C) | Excretion of 5-oxoproline has been found in patients with inborn errors of metabolism outside the γ-glutamyl cycle (e.g., homocystinuria, OCT deficiency, cystinosis) and in patients receiving certain drugs (vigabatrin, paracetamol) and specific diets (acid hydrolyzed protein formula). The combination of paracetamol and flucloxacillin may result in a fatal form of 5-oxoprolinuria. Urine glutamine may decompose to form 5-oxoproline |
| Mutation analysis (DNA sequencing) | – | FB, WBC, CV, AFC | Cells in culture (room temperature) | Prenatal diagnosis is greatly facilitated if the mutant allele in the specific family is known |

## 42.9 Prenatal Diagnosis

**Prenatal diagnosis is greatly facilitated if the mutant allele(s) in the specific family is known**

| Disorder | Tissue | Timing, trimester |
|---|---|---|
| **42.4.2** | CV | I |
| | AF | II |
| | AFC | III |

## 42.10 DNA Analysis

| Disorder | Tissue | Methodology |
|---|---|---|
| **42.3** | B, WBC, LYM | DNA sequencing |
| **42.4.1/2** | FB, WBC, LYM, CV, AFC | DNA sequencing |

## 42.11 Treatment

### Initial Treatment

Defects that lead to decreased levels of glutathione can be treated according to two complementary strategies: avoidance of drugs that lead to oxidative stress and supplementation with compounds that may act as free radical scavengers (e.g., vitamin C, vitamin E, and N-acetylcysteine).

The only disorder of the γ-glutamyl cycle for which treatment principles have been developed is glutathione synthetase deficiency (**42.4**) (Larsson and Anderson 2001). The initial symptoms in the neonatal period may be metabolic acidosis and jaundice. Acidosis usually needs to be corrected with sodium bicarbonate, THAM, or sodium citrate. Patients may benefit from oral administration of vitamin E (10 mg/kg/day) and vitamin C (100 mg/kg/day). Trials have also been made with N-acetylcysteine and glutathione esters which increased glutathione in leukocytes and plasma. Both these compounds lead to increased intracellular levels of glutathione. However, no decrease in the excretion of 5-oxoproline has been reported.

Patients who are deficient in γ-glutamylcysteine synthetase or glutathione synthetase should avoid drugs that can induce hemolytic crises in patients with glucose-6- phosphate dehydrogenase deficiency, e.g., phenobarbital, acetylsalicylic acid, and sulfonamides.

### Treatment Summary

For γ-glutamylcysteine synthetase deficiency, the recommended treatment is to avoid drugs and foods known to precipitate hemolytic crises in patients with glucose-6-phosphate dehydrogenase deficiency. Early supplementation with the antioxidant vitamins C and E seems to prevent damage to the CNS in patients with GSH synthetase deficiency (Ristoff et al. 2001). In analogy, supplementation with vitamins C and E might be worth testing also in patients with γ-glutamylcysteine synthetase deficiency. However, no studies of this treatment have yet been made.

Treatment of glutathione synthetase deficiency in the neonatal period involves the correction of acidosis and electrolyte imbalance and early treatment with the antioxidants vitamins E and C to prevent damage to the CNS (Ristoff et al. 2001).

The lesions in the brain of patients with GSH synthetase deficiency resemble those seen after intoxication with the toxic compound mercury, i.e., Minamata disease, and it has therefore been suggested that treatment with antioxidants may be beneficial (Skullerud et al. 1980). The goal of treatment in patients with GSH synthetase deficiency is to correct the acidosis and to compensate for the lack of antioxidant capacity in the cells. A long-term follow-up study of 28 patients showed that early supplementation with the antioxidant vitamins C and E is useful for preventing damage to the CNS in patients with GSH synthetase deficiency (Ristoff et al. 2001). Recommended treatment does not normalize the elevated excretion of 5-oxoproline in urine.

| No. | Disorder | Treatment/diet | Dosage (mg/kg/day) |
|---|---|---|---|
| **42.1** | γ-Glutamyl transpeptidase (GT) deficiency | No treatment has been recommended | |
| **42.2** | 5-Oxoprolinase deficiency | No treatment has been recommended | |
| **42.3** | γ-Glutamylcysteine synthetase deficiency | Avoid drugs and foods known to precipitate hemolytic crises in patients with glucose-6-phosphate dehydrogenase deficiency | |
| | | Vitamins C (ascorbic acid) | 100 |
| | | Vitamin E (α-tocopherol) | 10 |
| **42.4** | Glutathione (GSH) synthetase deficiency | Avoid the drugs and foods known to precipitate hemolytic crises in patients with glucose-6-phosphate dehydrogenase deficiency | |
| | | Correction of acidosis (bicarbonate, citrate, or THAM) | |
| | | Vitamin C (ascorbic acid)[a] | 100 |
| | | Vitamin E (α-tocopherol)[b] | 10 |

[a]A trial with short-term treatment of GSH synthetase-deficient patients with vitamin C has been reported to increase the levels of lymphocyte GSH (Jain et al. 1994). Vitamin C and GSH can spare each other in a rodent model (Martensson and Meister 1991)
[b]Vitamin E has been claimed to correct the defective granulocyte function (Boxer et al. 1979)

### Alternative Therapies/Experimental Trials

| No. | Disorder | Treatment/diet | Dosage (mg/kg/day) |
|---|---|---|---|
| **42.1** | γ-Glutamyl transpeptidase (GT) deficiency | No treatment has been recommended | |
| **42.2** | 5-Oxoprolinase deficiency | No treatment has been recommended | |
| **42.3** | γ-Glutamylcysteine synthetase deficiency | No treatment has been recommended | |
| **42.4** | Glutathione (GSH) synthetase deficiency | *N*-Acetylcysteine (NAC)[a] | 15 |
| | | Glutathione esters[b] | |

[a]Since *N*-acetylcysteine (NAC) protects cells in vitro from oxidative stress, it has been suggested that NAC supplements (15 mg/kg/day) should be given to GSH-deficient patients. However, today we know that patients with GSH synthetase deficiency accumulate cysteine and, in our opinion, NAC; therefore it should not be recommended (Ristoff et al. 2002)
[b]Glutathione esters have been tried in animal models of GSH deficiency and in two patients with GSH synthetase deficiency (Anderson et al. 1994) (W. Rhead 1995, personal communication). The GSH esters, which are more lipid soluble, are readily transported into cells and converted intracellularly into GSH. The esters increase GSH levels in several tissues, but their use is limited because of associated toxic effects, i.e., when they are hydrolyzed to release GSH; alcohols are produced as a by-product

### Follow-Up/Monitoring

| No. | Disorder | Clinical investigations | Laboratory investigations |
|---|---|---|---|
| **42.1** | γ-Glutamyl transpeptidase (GT) deficiency | Neurological investigations | |
| **42.2** | 5-Oxoprolinase deficiency | Neurological investigations | Acid–base balance |
| **42.3** | γ-Glutamylcysteine synthetase deficiency | Neurological investigations | Hb, reticulocytes |
| **42.4** | Glutathione (GSH) synthetase deficiency | Neurological investigation | Acid–base balance |
| | | Eye examination (retinal pigmentations, corneal opacities) | Hb, reticulocytes |

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