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Inherited Metabolic Disorders and Stroke Part 2

Homocystinuria, Organic Acidurias, and Urea Cycle Disorders

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Several inherited metabolic disorders have been associated with stroke particularly in newborns, children, and young adults. In part 1, we discussed the genetics, stroke pathophysiology, clinical presentation, diagnosis, and treatment of Fabry disease and mitochondrial myopathy, encephalopathy, lactic acidosis, and strokelike episodes. In part 2, we overview homocystinuria, organic acidurias, and urea cycle disorders.

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In part 1 of our review of inherited metabolic disorders and stroke, we addressed Fabry disease and mitochondrial encephalomyopathy with lactic acidosis and strokelike episodes syndrome (MELAS).[1] In part 2, we discuss homocystinuria, organic acidurias, and urea cycle disorders (UCDs).

HOMOCYSTINURIA

Genetics

The term *homocystinuria* refers to an increased urinary excretion of the oxidized form of homocysteine, homocystine. Classic homocystinuria is an autosomal recessive disorder caused by a deficiency of cystathionine β-synthase. This enzyme is encoded by chromosome 21, and more than 90 mutations of this gene have been described.[2] Classic homocystinuria is characterized by elevated levels of plasma homocysteine and its metabolite, methionine. Homocysteine level elevation with a normal methionine level may be caused by metabolic errors that affect the conversion of homocysteine to methionine such as methylene tetrahydrofolate reductase deficiency and disorders of cobalamin (vitamin B_{12}) metabolism (**Figure 1**).

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Epidemiology

Based on statistics of countries that consistently screen newborns, the estimated worldwide frequency of homocystinuria ranges from 1 case per 58 000 to 1 case per 1 000 000. Significant variability in the frequency of homocystinuria has been observed.[3]

Clinical Manifestations

Homocystinuria is a multisystemic disorder characterized by myopia, osteoporosis, mental retardation, decreased pigmentation of hair and skin, downward lens dislocation (ectopia lentis), and dolichostenomelia (tall thin individuals with thinning and lengthening of long bones) (**Table 1**). If left untreated, seizures, psychiatric disorders, and thromboembolic events (such as cerebral ischemia, myocardial infarction, and pulmonary embolism) may occur.[4] Clinically, the following 2 equally prevalent phenotypes have been described: a milder pyridoxal phosphate (vitamin B_6)–responsive form and a more severe pyridoxal phosphate–nonresponsive form.[4]

In a cohort of 629 patients diagnosed as having classic homocystinuria, thromboembolic events were reported in 25%.[4] Of 253 ischemic events, 51% were peripheral vein thrombosis (with one-quarter resulting in pulmonary embolism), 32% were strokes, 11% were peripheral arterial oc-

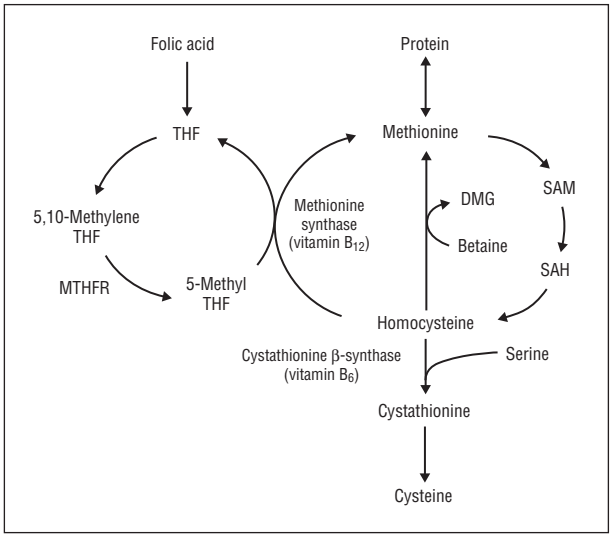

Figure 1. Metabolism of homocysteine and methionine. DMG indicates dimethyl glycine; MTHFR, methyl tetrahydrofolate reductase; SAH, *S*-adenosyl homocysteine; SAM, *S*-adenosyl methionine; and THF, tetrahydrofolate.

clusions, 4% were myocardial infarctions, and 2% were ischemic events in other areas.[4] In this cohort, the risk of having a vascular event was 25% before age 16 years and 50% by age 30 years. The treatment of pyridoxal phosphate responders with vitamin B_6 significantly delayed the occurrence of a first thromboembolic event.

Stroke Pathophysiology

Thromboembolism is the most common cause of death in classic homocystinuria, and different mechanisms have been proposed to explain this observation. Animal models and several observational investigations in humans have shown that an elevated serum homocysteine level is a risk factor for early atherosclerosis.[5] The latter finding may be further explained by experimental and clinical evidence suggesting that hyperhomocysteinemia causes endothelial dysfunction because of decreased bioavailability of the endogenous vasodilator nitric oxide and oxidative stress.[6-8] In addition, an underlying hypercoagulable state has been suggested based on enhanced thrombosis and platelet activation reported in animal models and in vitro investigations.[8] These changes may alter the stability of the arterial wall and explain the occurrence of intra-arterial thrombosis, arterial dissection, and arteriopathy mimicking fibromuscular dysplasia in young individuals with homocystinuria.[9,10]

Diagnosis

The diagnosis of homocystinuria is based on clinical presentation and laboratory studies. Screening for this disorder may be performed using a urinary cyanide nitroprusside test (Brand reaction). Typically, there is hyperhomocysteinemia, hypermethioninemia, and hypocysteinemia, and the urinary excretion of methionine, homocysteine, and its oxidized form (homocystine) is elevated. The activity of cystathionine β-synthase may be assessed in cultured fibroblasts, amniotic fluid, and chorionic villi cells. The responsiveness of cystathionine β-synthase to pyridoxal phosphate can be assessed in in vitro studies. However, this determination does not always correlate with the in vivo response of the patient to pyridoxal phosphate supplementation.[3]

Table 1. Clinical Manifestations of Homocystinuria

Organ	Manifestation
Skin	Hypopigmentation, malar flush, livedo reticularis
Central nervous system	Mental retardation, developmental delay, seizures, ischemic stroke
Psychiatric disorders	Personality disorder, behavior disorder, depression
Skeletal system	Osteoporosis, pectus excavatum or carinatum, genu valgum, scoliosis, dolichostenomelia with marfanoid appearance (rarely, arachnodactyly)
Eye	Extopia lentis, myopia, glaucoma, cataracts, retinal detachment, optic atrophy
Vascular system	Thromboembolism
Kidney	Foul odor of the urine
Gastrointestinal	Pancreatitis

Treatment

The main treatment goal in homocystinuria is to reduce, and if possible normalize, the plasma level of homocysteine. Pyridoxal phosphate supplementation is administered to enhance the metabolism of homocysteine to cysteine (Figure 1). This is achieved with administration of vitamin B_6 (300-600 mg/d). Supplementation with pyridoxal phosphate should be done judiciously to avoid development of peripheral neuropathy. In addition, folate, betaine, and vitamin B_{12} are used to promote metabolism of homocysteine to methionine. Because of abnormalities noted in the amino acid profile of these patients, a methionine-free diet supplemented with cysteine is recommended.[4]

Other treatments may include vitamin C, which was shown to ameliorate endothelial dysfunction in 5 patients with homocystinuria.[11] Antiplatelet agents are commonly administered for recurrent stroke prevention as it was shown to decrease mortality in patients with atherosclerosis and hyperhomocysteinemia.[11]

Outcome

The prognosis in homocystinuria is associated with the occurrence of vascular ischemia. Almost 25% of patients die before age 30 years. In a study[12] of 158 patients with cystathionine β-synthase deficiency who were treated for up to 18 years, treatment to lower the homocysteine level significantly reduced the risk of vascular events compared with historical control subjects. In a randomized controlled trial, Vitamin Intervention for Stroke Prevention,[13] an association between total homocysteine and vascular risk was demonstrated. However, reduction of serum homocysteine after nondisabling cerebral ischemia did not modify significantly the 2-year stroke rate when high-dose and low-dose vitamin B complex regimens were compared with placebo.[13]

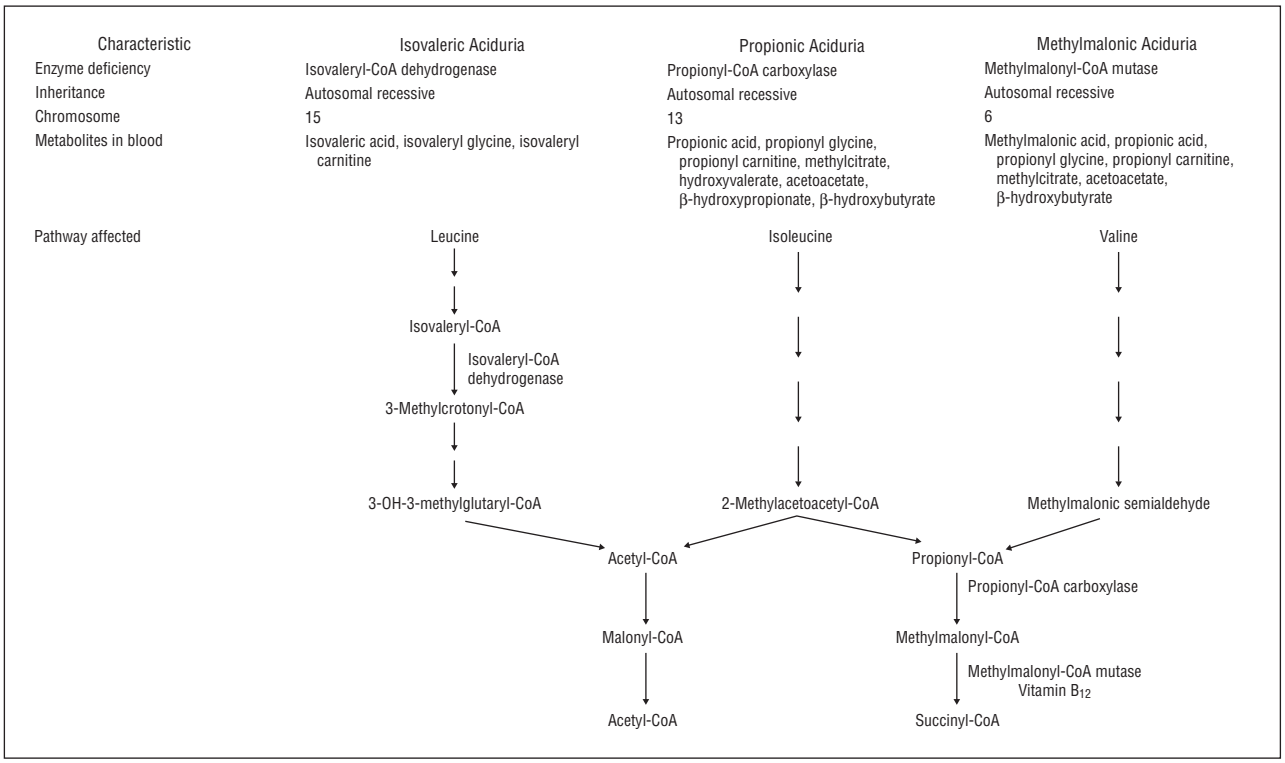

Figure 2. Branched-chain organic acidurias. CoA indicates coenzyme A.

ORGANIC ACIDURIAS

Branched-Chain Organic Acidurias

Genetics. Branched-chain organic acidurias (BCOAs) are inherited disorders of metabolism of branched amino acids and include isovaleric aciduria, propionic aciduria, and methylmalonic aciduria (**Figure 2**). The typical patient is from an uneventful pregnancy and normal delivery and has a variable initial symptom-free period of hours to weeks. Depending on residual enzyme activity, acute-onset neonatal and chronic infantile intermittent forms have been described.[14]

Clinical Manifestations. Patients with BCOAs may initially have nonspecific manifestations such as poor feeding, lethargy, dehydration, and vomiting. In the case of isovaleric aciduria, patients may have a distinctive "sweaty feet" odor during the acute illness caused by the accumulation of isovaleric acid. In laboratory analysis, there is evidence of anion gap acidosis, ketosis, hypocalcemia, hyperlactaciduria, and hyperammonemia. Serum glucose level may be normal, reduced, or elevated, and hematologic abnormalities (such as pancytopenia) are common. Other manifestations may include constipation, abdominal distention, pancreatitis, seizures, growth delay, cognitive impairment, and movement disorders (eg, tremors, choreoathetosis, and dystonia). Stroke manifestations are described in the next subsection.

Branched-chain organic acidurias can mimic other medical emergencies. For example, the constellation of hyperglycemia, ketoacidosis, and dehydration resemble diabetic ketoacidosis, and neutropenia, thrombocytopenia, or pancytopenia may occur with sepsis. Left untreated, patients with BCOAs progress to coma and death.[14]

Stroke Pathogenesis. Cerebellar hemorrhage has been described in isovaleric aciduria, propionic aciduria, and methylmalonic aciduria.[15,16] More typically, patients with propionic aciduria and methylmalonic aciduria have symmetric basal ganglia ischemic strokes, which may occur in the absence of metabolic decompensation and without other clinical manifestations.[17]

The pathogenesis of these lesions is largely unknown. Brain magnetic resonance spectroscopy studies[18,19] in children with propionic aciduria and methylmalonic aciduria have shown an increased content of lactate during metabolically stable periods, suggesting impaired aerobic metabolism and impending energy failure. Also, an elevation of the glutamine/glutamate peak on magnetic resonance spectroscopy has been observed in the basal ganglia of stable patients with propionic aciduria, suggesting an excess of glutamate, an excitatory neurotransmitter implicated in excitotoxicity and stroke.[20]

Diagnosis. The laboratory diagnosis of BCOAs depends on the results of plasma acyl carnitine and amino acid analyses and on urine acyl carnitine and organic acid profiles. Metabolic patterns found in different BCOAs are summarized in Figure 2 and have been reviewed by Zschocke and Hoffmann.[21] Diagnostic confirmation is carried out by enzyme assay in cultured fibroblasts or peripheral leukocytes. Molecular analysis may be performed, as genotype and phenotype relationships have been established. In pertinent

cases, prenatal diagnosis may be done using amniotic fluid or cultured amniocytes.[22]

Treatment. The treatment of BCOAs is complex. As a general principle, the goal is to prevent the formation of toxic metabolites. Protein restriction is adjusted judiciously to limit the intake of branched-chain amino acids while allowing protein synthesis and avoiding endogenous protein degradation. In addition, the diet is supplemented with L-carnitine to prevent its deficiency and to facilitate the synthesis of detoxifying acyl carnitine derivatives.[14] Because of a low incidence of BCOAs, there is limited information about specific stroke prevention and management for these patients. The use of aspirin in individuals with isovaleric aciduria is contraindicated, as salicylic acid may interfere with endogenous detoxifying mechanisms catalyzed by the enzyme glycine-*N*-acylase.[23]

Glutaric Aciduria Type 1

Genetics. Glutaric aciduria type 1 (GAT1) is an autosomal recessive disorder of metabolism of lysine, hydroxylysine, and tryptophan. It is caused by a deficiency in glutaryl coenzyme A dehydrogenase.[24]

Clinical Manifestations. About 75% of affected individuals have progressive macrocephaly. In neuroimaging studies, patients have frontotemporal atrophy, subependymal pseudocyst formation, and delayed myelination.[25] Also, there is stretching of bridging veins, predisposing to subdural hematoma, and retinal hemorrhages have been described.[24]

Patients with GAT1 are prone to acute neurologic crisis characterized by hypotonia or diffuse rigidity, encephalopathy, and dystonic posturing. Seizures may occur during acute metabolic decompensation, but epilepsy is uncommon. The encephalopathic crisis is usually precipitated by common childhood infections and is uniformly associated with striatal necrosis. Infectious illness, dehydration, and delay in initiation of treatment are risk factors for severe injury.[24]

Stroke Pathogenesis. The mechanism of striatal necrosis is not completely understood. The abrupt presentation and the presence of cytotoxic edema on magnetic resonance images are consistent with a strokelike mechanism.[24,26] Postmortem biochemical investigations have shown that the basal ganglia of patients with GAT1 contain high concentrations of glutaric acid and are deficient in glutamate decarboxylase and γ-aminobutyric acid, suggesting an excitotoxic mechanism.[27] In in vitro investigations, glutaric acid and its metabolite, 3-hydroxyglutaric acid, trigger apoptosis in immature oligodendroglial cells and endothelial cells.[28] These observations provide a mechanism to explain the abnormal myelination observed in GAT1 and suggest endothelial dysfunction.

Diagnosis. The laboratory diagnosis of GAT1 is based on the analysis of urinary organic acids and acyl carnitine profiles. The presence of elevated urine levels of glutaric and 3-hydroxyglutaric acids, as well as their acyl carnitine derivatives, suggests the diagnosis. These results should be confirmed by enzyme activity and mutational analysis. The detection of glutaryl carnitine in dried blood spot or in urine is used for newborn screening.[23,29]

Treatment. Management of these patients includes lysine-free and tryptophan-reduced diet with carnitine supplementation.[30] Riboflavin, a cofactor of glutaryl coenzyme A dehydrogenase, is usually administered in patients with GAT1. However, riboflavin responsiveness is rarely observed in clinical practice.

Glutaric Aciduria Type 2

Genetics. Glutaric aciduria type 2 (GAT2), also known as multiple acyl coenzyme A dehydrogenase deficiency, is an autosomal recessive disorder caused by deficiency in the electron transport flavoprotein or in the electron transport flavoprotein oxyreductase. Mutation of either enzyme impairs mitochondrial fatty acid β-oxidation and amino acid metabolism. The incidence and prevalence of GAT2 are unknown.[31]

Clinical Manifestations. Glutaric aciduria type 2 is characterized by metabolic decompensation triggered by stress. In laboratory studies, patients have acidosis, nonketotic hypoglycemia, hyperammonemia, and organic aciduria. There may be an odor of sweaty feet. In the neonatal form, patients may have congenital abnormalities such as microgyria, lung hypoplasia, facial dysmorphism, bilateral polycystic and dysplastic kidneys, and fatty degeneration of the heart, liver, and kidney.[31] Also, a late-onset milder form has been described and is characterized by lipid storage myopathy.[32] Symmetric hypoplasia of the temporal lobes with axonal loss and hypomyelination may occur in patients with GAT2.[33]

Stroke in a 3-year-old child with GAT2 has been described.[34] Because of the low incidence of GAT2, risk factors for and pathogenesis of stroke in this disorder have not been defined.

Diagnosis. The laboratory diagnosis of GAT2 is suggested by plasma acyl carnitine profile and urine organic acid analysis. Typically, patients with GAT2 have elevated creatine kinase levels in serum, as well as various combinations of elevated short-chain organic acid levels in the urine such as glutaric, 2-hydroxyglutaric, pyruvic, ethylmalonic, hippuric, adipic, and suberic. Plasma acyl carnitine profile shows an increase of all chain-length acyl carnitines. The diagnosis is confirmed by mutation and enzyme analysis.[23,35]

Treatment. Patients with GAT2 are treated with a low-fat, low-protein, and high-carbohydrate diet.[34] Supplements include carnitine and riboflavin.[35]

UREA CYCLE DISORDERS

Genetics. The urea cycle is an endogenous metabolic pathway that converts the toxic product of protein metabo-

lism, ammonia, into urea. This process occurs partly in the mitochondrion and partly in the cytoplasm of cells. It requires the participation of the cofactor *N*-acetylglutamate and 5 different enzymes (**Figure 3**). Several inborn metabolic errors affecting the urea cycle have been described (**Table 2**).

Clinical Manifestations. In severe cases, newborns with UCD have lethargy, poor feeding, and vomiting after initiating protein intake. Left untreated, patients may develop cerebral edema and progress to coma, seizure, and death. In the laboratory analysis, there is hyperammonemia without acidosis. In partial UCD deficiencies, hyperammonemia may be triggered by infection or stress at almost any time of life, and the symptoms are more subtle than in patients with early-onset UCDs. In a study[36] involving 260 patients with UCDs, the patient age at first hospitalization for hyperammonemia ranged from 1 day to 53 years, and approximately 20% of patients were older than 12 years. If measured outside of an acute crisis, the ammonia level may be slightly elevated or even normal.

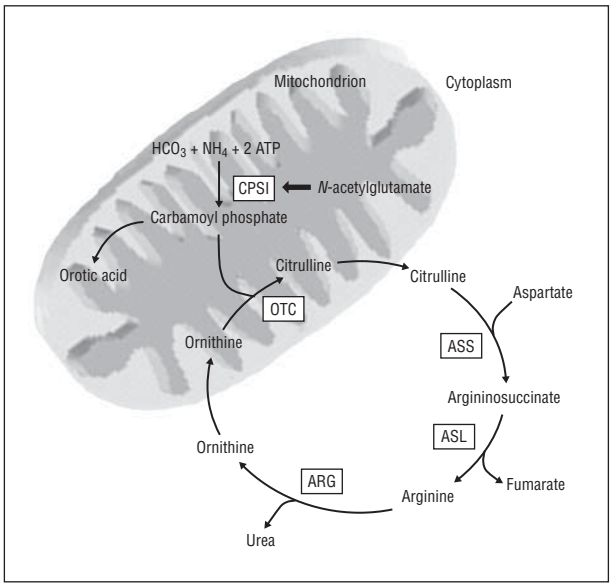

Figure 3. Urea cycle. ARG, arginase; ASL indicates argininosuccinic acid lyase; ASS, argininosuccinic acid synthetase; ATP, adenosine triphosphate; CPSI, carbamoyl phosphate synthetase I; and OTC, ornithine transcarbamylase.

Stroke has been described in individuals with ornithine transcarbamylase deficiency, carbamoyl phosphate synthetase I deficiency, and citrullinemia.[37-39] Also, strokelike episodes have been described in individuals with ornithine transcarbamylase.[40] In part because of the low incidence of these disorders, the pathogenesis of stroke in UCDs is not well defined.

Diagnosis. Analysis of plasma amino acid and urea cycle intermediates is useful in the diagnosis of UCDs. The metabolic profile depends on the specific biochemical defect (Table 2). The diagnosis can be confirmed by DNA and enzyme analysis.[41]

Treatment. The treatment is largely based on restriction of nitrogen intake and stimulation of alternative nitrogen excretion pathways. In the acute setting, a low-protein diet supplemented with essential amino acids is used, along with intravenous infusion of glucose to promote an anabolic state. In addition, patients are treated with arginine hydrochloride, sodium benzoate, and sodium phenylacetate infusion, which are intermediaries of alternative nitrogen excretion pathways. Peritoneal dialysis and hemodialysis may be considered in refractory cases.

Chronic management includes oral sodium benzoate and sodium phenylacetate supplementation, along with protein restriction. Liver transplantation may reverse the metabolic abnormality and has been shown to improve the neurologic outcome of individuals with ornithine transcarbamylase and carbamoyl phosphate synthetase I deficiency.[42] However, the effect of liver transplantation in the prevention of recurrent stroke has not been determined.[42]

In summary, in parts 1[1] and 2 of this review, we discussed proper identification, diagnosis, and treatment of inherited metabolic disorders that may cause stroke. Inherited metabolic disorders represent an uncommon but important causes of stroke primarily in neonates, children, and young adults. Recognition of these disorders is germane because they may be a previously unrecognized treatable or preventable cause of cryptogenic stroke.

Table 2. Urea Cycle Disorders

Subtype	Carbamoyl Phosphate Synthetase I Deficiency	Ornithine Transcarbamylase Deficiency	Citrullinemia	Argininosuccinic Aciduria	Argininemia
Enzyme deficiency	Carbamoyl phosphate synthetase I	Ornithine transcarbamylase	Argininosuccinic acid synthetase	Argininosuccinic acid lyase	Arginase
Inheritance	Autosomal recessive	X linked	Autosomal recessive	Autosomal recessive	Autosomal recessive
Chromosome	2	X	9	7	6
Prevalence	1:200 000 to 1:800 000	1:40 000 to 1:80 000	1:100 000	1:150 000	1:1 100 000
Metabolites	↑ Ammonia, ↑ glutamine and asparagine, ↓ citrulline, ↓ arginine	↑ Ammonia, ↑↑ orotic acid, ↑ glutamine and asparagine, ↓ citrulline, ↓ arginine, ↑ ornithine	↑ Ammonia, ↑ orotic acid, ↑↑ citrulline, ↑ or ↓ arginine	↑ Ammonia, ↑ orotic acid, ↑↑ argininosuccinate, ↑ citrulline	↔ Or ↑ ammonia, ↑ orotic acid, ↑ arginine

Abbreviations: ↔, Normal levels; ↓, reduced levels; ↑, elevated levels; ↑↑, markedly elevated levels.

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