Cobalamin Transport and Metabolism

Cobalamin (Cbl or vitamin B$_{12}$) is a cobalt-containing, water-soluble vitamin that is synthesized by lower organisms but not by higher plants and animals. In the human diet, its only source is animal products in which it has accumulated by microbial synthesis. Cbl is needed for only two reactions in man, but its metabolism involves complex absorption and transport systems and multiple intracellular conversions (Fig. 25.1). As methylcobalamin, it is a cofactor of the cytoplasmic enzyme methionine synthase. As adenosylcobalamin, it is a cofactor of the mitochondrial enzyme methylmalonyl-coenzyme A mutase, which is involved in the catabolism of valine, threonine and odd-chain fatty acids into succinyl-CoA, an intermediate of the Krebs’ cycle.

Fig. 25.1. Cobalamin (Cbl) endocytosis and intracellular metabolism. The cytoplasmic, lysosomal, and mitochondrial compartments are indicated. AdoCbl, adenosyl-Cbl; CoA, coenzyme A; MeCbl, methyl-Cbl; MS, methionine synthase; OHCbl, hydroxy-Cbl; TCII, transcobalamin II. 1’, 2’ and 3’ refer to the oxidation state of the central cobalt of Cbl. Letters refer to the sites of blocks [5]. Enzyme defects are indicated by solid bars.
Patients with inherited disorders affecting cobalamin (Cbl) absorption or metabolism show elevations of homocysteine or methylmalonic acid, either alone or in combination. For those disorders that affect methylcobalamin (MeCbl) formation, the major manifestations include megaloblastic anemia secondary to folate deficiency and neurological abnormalities presumably secondary to methionine deficiency or homocysteine elevation. For those disorders that affect adenosylcobalamin (AdoCbl) formation, the main findings are secondary to methylmalonic-acid elevations and resultant acidosis.

**COBALAMIN**

Inherited disorders of Cbl metabolism are classified as those involving absorption and transport and those involving intracellular utilization [1-5].

**Disorders of Absorption and Transport of Cobalamin**

Absorption of dietary Cbl involves first binding to a glycoprotein (R binder, haptocorrin, TCI) in the saliva. In the intestine, TCI is digested by proteases, allowing the Cbl to bind to intrinsic factor (IF), which is produced in the stomach by parietal cells. Using a specific receptor, the IF–Cbl complex enters the enterocyte. Cbl bound to transcobalamin II (TCII), the physiologically important circulating Cbl-binding protein, slowly enters the portal vein after release. Inherited defects of several of these steps are known.

**Hereditary Intrinsic Factor Deficiency**

**Clinical Presentation**

Megaloblastic anemia is the main finding [6-8]. It usually appears after the first year of life but before the age of 5 years. In cases of partial deficiency, clinical presentation has been delayed until adolescence or adulthood. The patients present with failure to thrive, often with vomiting and alternating diarrhea and constipation, anorexia and irritability. They are anemic and may have hepatosplenomegaly, stomatitis or atrophic glossitis, developmental delay, and myelopathy or peripheral neuropathy.

**Metabolic Derangement**

IF is either absent or nonfunctional. Some patients produce no IF whereas, in others, it may be detectable immunologically. There have been reports of IF with reduced affinity for Cbl, reduced affinity for the Cbl receptor or increased susceptibility to proteolysis [7-9].

**Diagnostic Tests**

The hematological abnormalities in the defects of Cbl absorption and transport should be detected by a measurement of red blood cell indices, a complete blood count and a bone-marrow examination. Megaloblastic anemia and a low serum Cbl are present. Homocystinuria and methylmalonic aciduria may be present. A deoxyuridine-suppression test on marrow cells is useful but is not easily available in most clinical laboratories. This test measures the incorporation of label from thymidylate (dTMP) in a trichloroacetic-