Hematologic Aberrations in Metabolic Diseases

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ABSTRACT

This study of enzyme deficiencies and hematologic aberrations in metabolic diseases includes disorders of amino acidopathies, lipid disease, albinism, carbohydrates, and mucopolysaccharidosis.

Introduction

The definition of metabolic disease has changed markedly during this century. When Sir Archibald Garrod gave the original Croonian lectures in 1902, metabolic disease was synonymous with the term "inborn errors of metabolism," but present concepts have expanded to include all diseases that affect availability of biological substrates or energy production. It would be impossible to summarize all the metabolic diseases that may have a primary or secondary effect on hematopoiesis; therefore, this study has been arbitrarily limited to diseases which have a known or postulated genetic enzyme deficiency as the primary aberration. Pathological states such as chronic liver disease, ingestion of toxins, or dietary deficiency states have not been considered within the scope of this text.

In table I are indicated the categories of enzyme deficiencies that present with clinical evidence of marked hematological aberrations. This list is divided into problems of amino acid metabolism, lipid disease, albinism, carbohydrate disorders and, finally, the mucopolysaccharidoses.

Amino Acidopathies
ACIDEMIAS

In 1971, Hsia described the enzyme deficiency that accounted for ketotic hyperglycinemia. Fibroblasts from patients with this disease were found to be deficient in propionyl CoA carboxylase activity, and the toxic product responsible for the clinical symptoms was propionic acid. Since this discovery, the disease is now referred to as propionic acidemia.

The dietary precursors of propionyl CoA and propionic acid are valine, leucine, isoleucine, methionine, threonine, cholesterol, and odd chain fatty acids. If these substances are drastically reduced in the diet, there is clinical and
biochemical improvement; unfortunately, exacerbations occur even when the patient strictly follows the diet.

Most patients with propionic acidemia present in the newborn period with severe metabolic acidosis, lethargy, hyperammonemia, and thrombocytopenia with neutropenia. The neutropenia responds to diet therapy with an increase in absolute polymorphonuclear neutrophil count. If diet therapy is discontinued, the neutropenia will recur, suggesting a toxicity of the metabolite propionic acid.13

In one patient the addition of large doses of biotin corrected the propionic acidemia with a concomitant normalization of the neutropenia.1

If propionyl CoA carboxylase is present, propionyl CoA is converted to methylmalonyl CoA and methylmalonic acid. The next step, conversion of methylmalonyl CoA to succinyl CoA, requires a mutase enzyme to convert the initial compound from the D-isomer to the L-isomer. Two abnormalities of this conversion have been described: one form is secondary to a racemase deficiency, and the other is secondary to a mutase apoenzyme abnormality. Adenosylcobalamin, from vitamin B12, is a cofactor for the mutase apoenzyme; two abnormalities of vitamin B12 conversion have caused clinically and biochemically similar pictures to the mutase deficiency. The dietary precursors of methylmalonic acid are the same as for propionic acidemia.

The lack of conversion of methylmalonyl CoA to succinyl CoA causes methylmalonic acidemia. This disease causes a clinical picture identical to propionic acidemia with severe neutropenia and thrombocytopenia in early infancy. The major hematologic difference is the fact that correction of the acidosis returns the white blood cell count and platelet count to normal in spite of continuing elevation of methylmalonic acid.17 This would suggest that the hematologic aberrations are secondary to the severe acidosis and not to direct product toxicity, as seen in propionic acidemia.

Metabolism of leucine can occur by the pathway described for the two previous diseases, but there is an alternate pathway which converts leucine to ketoisocaproic acid. The next step is decarboxylation of ketoisocaproic acid to isovaleryl CoA, and

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**TABLE I**

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then oxidation to methylcrotonyl CoA by isovaleryl CoA dehydrogenase. The absence of this enzyme causes isovaleric acidemia. This disease is characterized by vomiting, acidosis, severe neurologic symptoms, a smell of "sweaty feet," and severe leukopenia with anemia and thrombocytopenia. The hematologic abnormalities improve with therapy but return during periods of relapse with acidosis.

The consistent finding of acidosis and leukopenia with thrombocytopenia in isovaleric acidemia, propionic acidemia, and methylmalonic acidemia raises the question of cause and effect. The evidence against acidosis as the sole cause of leukopenia is the finding of normal hemograms during severe episodes of maple syrup urine disease, hyperammonemia, and lactic acidosis. These diseases create similar systemic acidosis to the former diseases, but no effects on hematopoiesis are noted.

Sulfur Compound Abnormalities

Cystathionine synthetase deficiency causes classical homocystinuria. The sulfur containing methyl donor compound S-adenosylmethionine is the precursor for S-adenosylhomocysteine which is converted to homocysteine and then to cystathionine by cystathionine synthetase. The initial compound in the sulfur pathway is derived from ATP and the essential amino acid methionine.

Homocystinuria

Classical homocystinuria is characterized by ectopia lentis (dislocated lenses), osteoporosis, biconcavity of the vertebrae, tall stature, thin habitus, mental retardation in 80 percent of the patients, and recurrent thromboembolism. It is generally accepted that the vascular complications of this disease are the cause of mental retardation as evidenced by the multiple brain infarcts in affected individuals. Extensive research efforts attempting to identify the cause of thromboembolism have failed to identify the offending metabolite and there is conflicting evidence that platelet adhesiveness is increased in affected individuals.

Unpublished work,* attempted to induce platelet aggregation with methionine and homocystine in vitro. If the sample were acidic, aggregation would occur with either metabolite; otherwise, platelet abnormalities did not appear. Our laboratory was unable to find any primary defect in platelets from patients with homocystinuria. Recently, Harker demonstrated decreased platelet survival time in patients with homocystinuria. These findings were then duplicated in baboons by creating vascular wall desquamation with homocystine infusions. At the present time, this finding strongly points to a vascular abnormality causing thromboembolism instead of primary platelet abnormalities.

Dietary therapy limiting methionine reduces the incidence of thromboembolism but does not eliminate it. In 50 percent of the patients, pyridoxine (vitamin B6) reduces or eliminates the need for diet therapy. The exact mechanism of pyridoxine effect is not yet understood.

In 1969, Mudd described a patient with homocystinuria who excreted large quantities of methylmalonic acid. Investigations revealed that this patient had an inability to metabolize B12 intracellularly. The clinical constellation was similar to classic homocystinuria, but the patient had normal cystathionine activity. The hematologic aberrations in this disease were different because there was no evidence of thromboembolism but there was marked megaloblastic anemia which did not correct with large doses of vitamin B12. There are two other forms of homocystinuria that have been described, but there is no evidence of thromboembolism or anemia in these diseases.

* In collaboration with Dr. Owen Rennert.
Cystathionuria

Absence of cystathionase, the next enzyme in the homocystine pathway, causes cystathionuria. This disease has a very inconsistent clinical picture, and there is controversy as to whether or not it causes any significant clinical disease. One case of thrombocytopenia has been associated with an absence of cystathionase activity.11

Glutathione Deficiency

Two patients have been described with hemolytic anemia secondary to glutathione deficiency. The anemia was associated with aminoaciduria, spino-cerebellar degeneration, peripheral neuropathy, and myopathy. Enzyme analysis of red blood cells revealed less than 3 percent activity of γ glutamylcysteine synthetase.7 It has been postulated that the γ glutamyl cycle is involved in amino acid transport, and this blockade may be the cause of the hemolytic anemia as well as the aminoaciduria.

Another group of patients has been described with glutathione synthetase absence and decreased glutathione production. The patients have had acidosis and hemolytic anemia with 5-oxoprolinuria. Erythrocytes and fibroblasts from these patients had deficient enzyme activity and very low glutathione concentrations. Finally, a third group of patients has been investigated because of hemolytic anemia in the absence of any other symptoms. These patients had deficient glutathione synthetase only in the erythrocyte, the rest of their tissues had normal levels.14 The erythrocyte deficiency of glutathione is postulated to cause the hemolytic anemia.

Hartnup's Disease

Amino acids are absorbed from the jejunum and reabsorbed from the kidney by specific carriers. It appears that there are six separate carriers, and specific groups of amino acids are absorbed by each carrier. The carrier of monoamino–monocarboxylic acids is greatly reduced in Hartnup's disease; therefore, renal loss of these compounds occurs along with poor jejunal absorption. Owing to decreased intestinal absorption, monoamino–monocarboxylic acids remain in the gut and bacterial conversion of these amino acids occurs. Tryptophan provides the majority of abnormal compounds,—specifically, indican, indolylacetic acid, and indolylacryloylglycine. With the decrease in tryptophan absorption, there is a lack of substrate for production of nicotinamide (niacin).18

Clinical symptoms of Hartnup's disease include cerebellar ataxia and pellagra (niacin deficiency) with secondary diarrhea and anemia. The neurological symptoms improve with antibiotic gut sterilization, probably limiting toxic products from bacterial conversion of unabsorbed amino acids. Pellagra and diarrhea improve with the addition of large quantities of oral nicotinamide. The hypochromic anemia improves when the pellagra symptoms are treated, but a mild suppression of red blood cell production continues even after long term therapy. Owing to poor monoamino–monocarboxylic acid absorption, serum levels of these amino acids are low and may account for the chronic anemia. General prognosis is good, although some patients show residual neurological symptoms.

Histidinemia

The clinical findings of histidinemia are variable, but speech defects and mental retardation have occurred in over 50 percent of patients found. Some patients are totally asymptomatic in spite of high levels of serum histidine. Several hematologic aberrations have occurred, but it is difficult to ascertain if these findings are random or associated. Throm-
bocytopenia purpura occurred in one patient and the platelet abnormalities improved with institution of diet therapy. Anemia has occurred on occasions.4

The absence of histidase activity in skin fibroblasts and liver biopsy is consistent with the elevation of serum and urine histidine levels in these patients.

PKU

Phenylketonuria is due to total or partial loss of the enzyme phenylalanine hydroxylase. Diet therapy lessens the severity of mentation defects, decreases the severe skin rash, and improves the general nutritional state of the patient. Dietary therapy requires continual monitoring of serum phenylalanine levels to keep the value below 10 mgm per dl, but greater than 4 to 5 mgm per dl, whereas normal levels in unaffected individuals are 2 to 3 mgm per dl. If therapy is not monitored closely, phenylalanine deficiency may occur. The sequelae of phenylalanine deficiency includes aminoaciduria, hypoglycemia, and megaloblastic anemia. The anemia responds to replacement of phenylalanine in levels greater than 3 mgm per dl.15

OROTIC ACIDURIA

The presence of severe megaloblastosis and hypochromic anemia, which is resistant to standard iron plus folate therapy, are the hallmarks of orotic aciduria. This probable autosomal recessive disease appears to involve deficiencies of the two sequential pyrimidine enzymes, orotidine-5-phosphate decarboxylase and orotate phosphoribosyltransferase. In the absence of these enzymes, large quantities of orotic acid are formed and excreted in the urine.

Presently, there are only nine described patients with orotic aciduria, but their clinical presentations have been similar. The patients have been diagnosed in the first year of life because of failure to thrive, retarded motor development, crystalluria with ureteral obstruction, hypochromic anemia, leukopenia, and a megaloblastic bone marrow which does not respond adequately to large doses of folate. In the absence of enzyme studies of the leukocyte pyrimidine pathway, the diagnosis can be confirmed by the presence of large amounts of orotic acid in the urine, and a clinical remission of the megaloblastosis following oral uridine therapy. The presence of orotic acid in the urine is not diagnostic since urea cycle enzyme deficiencies and allopurinol therapy can produce orotic aciduria.

The explanation of a single gene producing a deficiency of two enzymes remains obscure, but suggests a mutation of the operant control locus in this disease.

LIPID DISEASES

SPHINGOLIPIDOSTROPHIES

Sphingolipids are found in membranous tissues throughout the body. They share a common base structure of the amino alcohol sphingosine, with a long chain fatty acid bond at carbon 2; this structure is called ceramide. The hallmark of these diseases is the lack of a hydrolytic enzyme necessary for catabolism of a specific sphingolipid. Niemann-Pick, Gaucher's, and Fabry's disease are in this category, and they cause similar hematologic aberrations.

NIEMANN-PICK DISEASE

Niemann-Pick disease is caused by a deficiency of sphingomyelinase with a build up of tissue sphingomyelin. Clinical findings include hepatosplenomegaly, pulmonary infiltrates, and varying degrees of nervous system involvement. Hematologic abnormalities are consistent with hypersplenism, specifically, microcytic anemia, and thrombocytopenia. The bone marrow contains characteristic "sea-blue histiocytes," but the blood-
forming cells of the marrow appear to be normal. The "sea-blue histiocytes" in this disease contain lipid inclusions which appear laminated with electron microscopy.3

GAUCHER'S DISEASE

Gaucher's disease is characterized by absence of the enzyme glucocerebrosidase and the elevation of glucocerebroside in various organs and tissues. Clinical symptoms include hepatosplenomegaly, bone pain, pathologic fractures of the femur, hip joint collapse, CNS involvement in the infantile and juvenile forms, elevated acid phosphatase, and often severe hematologic emergencies. Hypersplenism occurs in nearly 100 percent of the patients causing thrombocytopenia, epistaxis, purpura, hemorrhagic infarcts, and gastrointestinal bleeding. These problems are corrected by splenectomy, but this may hasten liver and bone involvement.10 The bone marrow contains characteristic lipid laden histiocytes which stain for carbohydrate with periodic acid Schiff reagent. Microscopic appearance is different from "sea-blue histiocytes" owing to the appearance of "crinkled tissue paper" or "crumpled silk" in the cytoplasm. These cells do not appear to cause loss of the normal blood-forming cells in the marrow.

FABRY'S DISEASE

Fabry's disease demonstrates deficient activity of galactosidase with systemic deposition of globotriaosylceramide. Clinical symptoms include a raised scrotal lesion (x-linked disease), pain in the extremities which improves with Dilantin, hypohidrosis, lymphedema, severe kidney disease, and anemia. The anemia is due to decreased red blood cell survival,8 and late in the disease is secondary to the renal disease. There are lipid-laden macrophages in the bone marrow but these do not appear to affect the erythropoietic system.

CHOLESTEROL ESTER STORAGE DISEASE

There are two distinct phenotypic expressions of deficient acid lipase activity: cholesterol ester storage and Wolman's disease. Wolman's occurs in infancy with hepatosplenomegaly, steatorrhea, adrenal calcifications, anemia, and death; whereas, cholesterol ester storage is detected in adults with widespread lipid deposition, elevated triglycerides and cholesterol esters, hepatomegaly, and premature atherosclerosis. Microcytic, hypochromic anemia is common, but the mechanism is obscure. The bone marrow can contain foam cells, but the blood-forming tissues appear normal.

FAMILIAL LECITHIN-CHOLESTEROL ACYL TRANSFERASE DEFICIENCY

This rare disease is characterized by renal failure, corneal opacity, hyperlipidemia, and hemolytic anemia. The enzyme deficiency is the acyl transferase causing the increased serum and tissue lipids. The anemia is due to hemolysis, presumably secondary to accumulation of cholesterol and phospholipids on the red cell membrane. The lipid content of the red blood cell causes the appearance of "target cells" which clear in normal plasma.2 The bone marrow contains nonspecific "foam cells." Dietary therapy has not yet been successful in preventing these sequelae.

BASSEN-KORNZWEIG DISEASE

Abetalipoproteinemia demonstrates fat malabsorption, ataxic neuropathy, diarrhea, retinitis pigmentosa, and acanthocytosis with anemia. Very low density lipoprotein (VLDL) fractions, low density lipoprotein (LDL) fractions, and chylomicrons are absent from the serum,
presumably owing to absent triglyceride transport. The anemia is probably due to general malnutrition, and it is reversible with parenteral iron with folate therapy. The confusing phenomena is acanthocytosis; no explanation has been accepted for their presence in this disease. In defibrinated blood, autohemolysis occurs in 40 percent of the acanthocytes; autohemolysis can be reversed by addition of LDL and high density lipoprotein (HDL) lipid fractions.\textsuperscript{19} No clinical sequelae of this phenomena have been noted. Vitamin E therapy improves the neurologic symptoms.

Whatever the defect is in HPS, the presence of white blood cell inclusions and albinism should alert the clinician to the bleeding diathesis associated with platelet aggregation abnormalities.

CHS is a rare form of albinism associated with early childhood infection, progressive neuropathy, lymphoreticular malignancy, anemia, neutropenia, thrombocytopenia and peroxidase-positive lysosomal granules in the leukocytes. Death occurs prior to age 20. No etiology is known and few studies have been done on these patients.

Albinism

The term albinism encompasses that group of disorders exhibiting ocular or oculocutaneous hypomelanosis. The metabolic defect is in the melanocyte of the eye and skin, which appear to be normally distributed in human albinos. The site of enzymatic disturbance is the pathway producing melanin and occasionally involves tyrosine conversion steps. There are three distinct ocular types and seven oculocutaneous syndromes.

The two syndromes associated with hematologic aberrations are Hermansky-Pudlak (HPS) and Chediak-Higashi (CHS) syndromes. HPS patients have oculocutaneous albinism with hemorrhagic episodes, bruising, prolonged bleeding during tooth extraction, and hemoptysis. A great deal of investigation has been directed at the basic abnormality in HPS, but the exact etiology is still undetermined. The presently popular theory is an aberration in prostaglandin synthesis in the platelet.\textsuperscript{20} Platelets are definitely abnormal in function and no other hematologic defect can be found.

Pigment laden macrophages which stain blue with azure dye are found in the bone marrow, while peripheral leukocytes contain ceroid-like inclusions or membrane bound dense bodies.

Carbohydrate Disorders

GLYCOGEN STORAGE DISEASE TYPE I (VON GIERKE'S)

This disease is included because clinicians associate this disorder of glucose-6-phosphatase with skin bleeding and mild anemia. The studies indicate no abnormalities of hematologic function in spite of chronic acidosis. The skin bleeding is secondary to vascular fragility which appears to be a function of the severity of liver disease. The anemia also correlates with the liver disease. The vascular problems do not appear to be a primary consequence of altered glycogen release.

Galactosemia

This abnormality of galactose-1-phosphate uridyl transferase is characterized by early onset vomiting, diarrhea, jaundice, failure to thrive, mental retardation, and severe hemolysis resembling erythroblastosis. The hemolysis can be a terminal event in these patients. The exact cause of hemolysis is unknown, but red blood cells from patients with galactosemia have impaired oxygen uptake and possible decreased adenosine triphosphate availability.\textsuperscript{16} Diets free of galactose can reverse the process noted including the hematological aberrations.
Mucopolysaccharidosis

Finally, a brief statement to reiterate the fact that in spite of severe storage defects, hepatosplenomegaly, and bone damage, these patients show no aberrations of the hematological system until late in the disease. The only hematological problems in these patients is when the liver disease has reached terminal stages. The patient then becomes anemic and has decreased clotting factors. Hypersplenism is not seen in this disease complex.

References