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Acute and Chronic Pancreatitis in Patients with Inborn Errors of Metabolism

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Abstract
Acute and chronic recurrent pancreatitis have been reported in patients with a variety of inborn errors of metabolism. Among these are hyperlipidaemias, various disorders of branched-chain amino acid degradation, homocystinuria, haemolytic disorders, acute intermittent porphyria and several amino acid transporter defects. Some of these disease entities are exceedingly rare. In most of these disorders, pancreatitis is not very common and, with the exception of lipoprotein lipase and apolipoprotein C-II deficiency, is neither the leading nor the clinically most distressing manifestation of the underlying metabolic defect. The majority of these syndromes are, however, inherited, and often entire kindreds are carriers of well-defined germline mutations that can, to varying degrees, be associated with pancreatitis. We have reviewed the clinical, biochemical and genetic characteristics of those inborn errors of metabolism because interesting information can be gained from them in regard to the pathophysiology of pancreatitis and because they need to be distinguished from other hereditary causes of the disease.

Pancreatitis Caused by Hyperlipidaemia

Hyperlipidaemia is one of the most common inherited causes of recurrent pancreatitis. A number of familial disorders, including lipoprotein lipase deficiency, apolipoprotein C-II deficiency and common hypertriglyceridaemia, can result in massive plasma accumulations of chylomicrons or triglycerides. Triglyceride levels above 2,000 mg/dl are generally considered to put patients at a significant risk of developing pancreatitis.

Hereditary Lipoprotein Lipase Deficiency

Lipoprotein lipase is a glycoprotein serine esterase that forms homodimers at the luminal surface of endothelial cells. The human gene has 10 exons and is located on chromosome 8p22. Lipoprotein lipase activity at the endothelial membrane together with its co-factor apolipoprotein C-II, which is contained in chylomicrons, are major components in the processing of circulating lipo-

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proteins. Lipoprotein lipase deficiency as a cause of hyperlipidaemia was first reported in 1960, and in the meantime, more than 30 disease-relevant mutations have been reported. The mode of inheritance is autosomal recessive and the disease has a low incidence of 1/1,000,000, but is more frequent in parts of Canada and areas of the world where consanguinity is common. The first symptoms often arise in early childhood and the most common clinical presentation includes abdominal pain caused by recurrent attacks of pancreatitis, eruptive cutaneous xanthomatosis and hepatosplenomegaly. Almost 30% of patients with lipoprotein lipase deficiency develop pancreatitis. Another characteristic clinical finding is the presence of eruptive xanthomas. These are lipid deposits in the patient's skin that most commonly affect the buttocks, knees and extensor surfaces of the arms. They can become generalized but disappear over a period of months under effective lipid-lowering therapy. Recurrence of xanthomas is regarded as a sign that triglyceride-lowering therapy is inadequate.

Lipoprotein lipase deficiency should be suspected in hyperlipidaemic patients when chylomicrons are detectable in refrigerated fasting plasma and no significant very-low-density lipoprotein (VLDL) elevation is found. The diagnosis of lipoprotein lipase deficiency can be made by measuring the enzyme activity in post-heparin plasma (heparin releases the enzyme into the bloodstream) with a commercially available ELISA. Heterozygous carriers of mutations in the lipoprotein lipase gene generally have a lower catalytic activity than wild-type controls. The diagnosis can be confirmed by molecular genetic techniques which identify the mutation. The disease is not associated with atherosclerotic vascular disease and its most prominent clinical feature is recurrent pancreatitis. The variety of pancreatitis associated with lipoprotein lipase deficiency is most often recurrent, sometimes severe and necrotizing and only rarely leads to diabetes, pancreatic calcifications or exocrine pancreatic deficiency. Young patients learn to prevent the abdominal pain by avoiding foods with high fat contents. The laboratory diagnosis of pancreatitis can be difficult because chylomicrons may interfere directly with the measurement of amylase, haemoglobin and bilirubin. Amylase levels in patients with pancreatitis caused by lipoprotein lipase deficiency can be lower than expected or even normal, whereas hyperbilirubinaemia (as seen also in Zieve's syndrome) can appear without clinical relevance. The association between pancreatitis and hypertriglyceridaemia has long been known, but the former was long considered to be the cause of the latter. It is now well established that the opposite is true, and hyperlipidaemia is regarded as a well-established cause of pancreatitis [1–3] and can account for up to one quarter of hospital admissions for pancreatitis [2–4]. The severity of pancreatitis in patients with lipoprotein lipase deficiency can vary greatly and is not always paralleled by a proportionate chylomicronaemia. As mentioned above, even patients with severe necrotizing pancreatitis have been admitted with normal or only mildly elevated amylase levels, because hyperlipidaemia interferes with amylase measurements, leading to false-negative results [1, 2, 5–8]. The treatment of pancreatitis in these patients is not different from that with other causes of the disease, but an aggressive lipid-lowering therapy by dietary restriction of fat intake is paramount to prevent recurrence. Both animal and vegetable fat intake should be lowered to 15% of calories with the goal of lowering plasma triglyceride levels to below 1,000 or 2,000 mg/dl. Medium-chain triglycerides can serve as a substitute because they are not incorporated into chylomicrons after absorption. Parents of affected children need to be counselled about the benefits of medium-chain triglyceride fats and their initially inferior taste, as well as the fact that unsaturated as well as saturated fat must be restricted. Other important counselling factors are the requirements for extremely aggressive fat-lowering strategies during pregnancy, the futility of fat-lowering drugs and the avoidance of agents that increase endogenous triglyceride levels, such as alcohol, estrogens, diuretics, isotretinoin and beta-blockers [9–15].

Apolipoprotein C-II Deficiency

Apolipoprotein C-II deficiency was first reported in 1978, is inherited as an autosomal recessive disorder with a worldwide distribution and results in an impaired clearance of chylomicrons from the blood. The gene for apolipoprotein II-C is located on chromosome 19 and has four exons. The enzyme belongs to a family of apolipoproteins with other known members such as apolipoproteins E and C-I on chromosome 19 and apolipoproteins A-I, C-III and A-IV on chromosome 11. Apolipoprotein C-II deficiency is less common than lipoprotein lipase deficiency, and more than 10 disease-relevant mutations in the apolipoprotein C-II gene have been reported. All affected patients were homozygous carriers. Apolipoprotein C-II is synthesized in the liver and secreted in great abundance into the plasma. The most prominent function of apolipoprotein C-II is that as an activator for lipoprotein lipase. The enzyme recycles between high-density lipoprotein and the triglyceride-rich lipoproteins, chylomicrons and VLDL

and plays a gatekeeper function for lipid metabolism and energy storage. It regulates the hydrolysis of triglycerides in the core of lipoproteins, which results in free fatty acids.

Apolipoprotein C-II deficiency is generally diagnosed later than lipoprotein lipase deficiency in older children or young adults and the most frequent clinical presentation is that of recurrent episodes of pancreatitis. The diagnosis is made by measuring lipoprotein lipase activity in post-heparin plasma as described above or on gel electrophoresis of VLDL apolipoproteins. A distinction from lipoprotein lipase deficiency can be readily made because the addition of apolipoprotein C-II to the assay completely restores lipolytic activity but does not affect the plasma of patients with lipoprotein lipase deficiency.

A transfusion of normal plasma into a patient with apolipoprotein C-II deficiency results in a rapid decease in plasma triglyceride levels and can even be used therapeutically when aggressive lipid-lowering therapy is indicated for an episode of severe pancreatitis. Clinically, apolipoprotein C-II deficiency resembles lipoprotein lipase deficiency, but generally has a milder course and later onset of symptoms (between 13 and 60 years).

However, pancreatitis represents a more frequent and sometimes severe complication of apolipoprotein C-II deficiency, and up to 60% of patients are affected by episodes of pancreatitis [16–18]. If lipid-lowering treatment is not initiated early, pancreatitis can result in chronic exocrine and endocrine pancreatic insufficiency. As in patients with lipoprotein lipase deficiency, premature atherosclerosis is not a clinical feature of the disease.

The treatment of apolipoprotein C-II deficiency is similar to that of lipoprotein lipase deficiency and consists in restricting the dietary intake of fat. The lipid-lowering therapy can often be less aggressive than for patients with lipoprotein lipase deficiency because of the milder phenotype and the less dramatic increase in plasma triglycerides. Heterozygote carriers have an approximately 50% reduction in aplipoprotein C-II activity, but because only 10% of aplipoprotein C-II is physiologically required for the clearance of chylomicrons from the plasma, these patients have normal circulating lipid levels.

Familial Hypertriglyceridaemia and Chylomicronaemia

Several other disorders of lipid metabolism have been reported that can lead to either chylomicronaemia or hypertriglyceridaemia and are not associated with defects in the lipoprotein lipase system. As shown for lipoprotein lipase deficiency and apolipoprotein C-II deficiency, they represent a significant risk factor for the development of acute or recurrent pancreatitis when plasma triglyceride levels rise above 2,000 mg/dl. The incidence of patients with lipid disorders that result in such elevated triglyceride levels is estimated to be between 10 and 20/100,000 and is therefore much higher than that of disorders caused by inborn errors of the lipoprotein lipase system. Often, the high triglyceride levels are not caused by the disorder alone, but are precipitated by additional factors such as diabetes mellitus, alcohol, beta-adrenergic blockers, glucocorticoids and estrogens, diuretics and other drug therapies. All of these factors can greatly increase the extent of hypertriglyceridaemia and raise it above the threshold level for developing pancreatitis. The most common familial disorders associated with chylomicronaemia are the type I and type V hyperlipoproteinaemias (according to Levy and Fredrickson [18]). They comprise a diverse group of primary and secondary disorders with moderate to severe hypertriglyceridaemia. Individuals with monogenic familial hypertriglyceridaemia are rare and often have only mild hypertriglyceridaemia, and the abovementioned additional factors are often required before the risk of developing pancreatitis becomes significant. Unrelated diseases that have been found to increase plasma lipids in these predisposed patients are plasmocytoma, systemic lupus erythematosus and lymphomatous disease. In terms of therapy, most patients will require a low-fat diet. In addition, and in contrast to lipoprotein lipase or apolipoprotein C-II deficiency, lipid-lowering drugs can be effective.

Glycogen Storage Disorders

In Europe, the incidence of glycogen storage diseases is approximately 1/20,000. The first patient with 'hepatonephromegalia glycogenica' was described by von Gierke in 1928. Since that initial description, over 10 different disease varieties involving disturbances of glycogen metabolism have been described and they can present with a wide spectrum of clinical symptoms. The liver and striated muscles store most of the body's glycogen and are therefore most commonly affected by inborn errors of glycogen metabolism.

Acute and chronic pancreatitis have been reported in patients with type I (von Gierke) glycogen storage disease [19–21]. The underlying mechanism for the development of pancreatitis in these patients is not known, but the most

common biochemical changes in this disease variety include hypoglycaemia, lactic acidosis, hyperuricaemia and hyperlipidaemia – any of which could contribute to the onset of pancreatitis. Although the liver is most prominently affected (hepatomegaly due to excessive storage of glycogen and fat), other organs, including the kidneys (nephrocalcinosis and proteinuria) and the intestinal mucosa (intermittent diarrhoea), can be involved in addition to the pancreas. Most patients are diagnosed in early childhood (3–5 months) and present with hypoglycaemia, lactic acidosis or hepatomegaly. Fat and glycogen deposits can be detected in some patients as skin xanthomas over the arms and legs or as yellowish lesions on the retina. Impaired platelet aggregation leads to recurrent epistaxis and frequent bruising and may also contribute to a haemorrhagic course of acute pancreatitis. Clinical symptoms often deteriorate during pregnancy in affected women but fertility appears to be normal. Glycogen storage disorder type I is caused by a deficiency of glucose-6-phosphatase. The most frequent disorder is glycogen storage disorder Ia, due to a defect in the glucose-6-phosphatase gene, whereas a glucose-6-phosphatase translocase is deficient in glycogen storage disorder Ib. Disease-causing mutations have been identified in both of these genes. The aim of therapeutic approaches is the maintenance of normal concentrations of blood glucose, since normoglycaemia leads to a normalization of nearly all disease-associated abnormalities. In general, most affected patients receive frequent meals with a high carbohydrate content and restriction of galactose and fructose during the day and nocturnal nasogastric infusions, leading to an impressive improvement in the clinical outcome.

Branched-Chain Ketoaciduria (Maple Syrup Urine Disease)

Branched-chain ketoaciduria or maple syrup urine disease (MSUD) is an autosomal recessive disorder with an incidence of between 0.5 and 1/100,000 in the Western world. Cases of MSUD have been reported from virtually every ethnic group and the incidence is much higher than indicated above in countries where a ban on consanguineous marriages is not legally or socially enforced (some Middle Eastern and Asian nations). The highest rate of MSUD has been reported from isolated and highly inbred societies such as Pennsylvania Mennonites and Amish (1/180). The first cases of central nervous degeneration and death in early childhood due to deficient branched-chain amino acid metabolism were reported in 1954 by Menkes and co-workers, and because the urine of these children had a peculiar smell that was reminiscent of maple syrup or burned sugar, the disease was called 'maple syrup urine disease'. The odour was later found to be caused by urinary excretion of branched-chain ketoacids (2,4-dinitrophenylhydrazones) derived from greatly elevated serum levels of the branched-chain amino acids leucine, isoleucine and valine.

This observation suggested that the catabolism of branched-chain amino acids was blocked and the respective α-ketoacids [1–14C] did not undergo decarboxylation (branched-chain ketoaciduria).

Between the late 1970s and the late 1980s, not only the enzyme responsible for ketoacid breakdown (branched-chain α-ketoacid dehydrogenase) but also its molecular structure, composed of three catalytic components and two regulatory enzymes that are encoded by six genetic loci, were identified. A variety of deletions, insertions and frameshift mutations in these loci have been found to be associated with the MSUD phenotype. Today, sequencing of the most commonly affected catalytic subunits E1a, E1b, E2 and E3 permits prenatal and carrier detection in many cases. Five clinical and biochemical phenotypes of branched-chain aminoaciduria are distinguished: classic, intermediate, intermittent, thiamin-responsive and dihydrolipoyl dehydrogenase-deficient MSUD. Patients with classic MSUD have the most severe phenotype. Due to the accumulation of leucine and ketoisocaproic acid, they present with a neonatal onset of encephalopathy, seizures, coma and rapid weight loss which leads to death if treatment is not initiated immediately and severe neurologic damage in surviving patients. Pancreatitis has been reported in patients with several organic acidaemias, including MSUD [22, 23].

Patients with intermediate MSUD have residual enzyme activity of up to 30% and, because of their milder phenotype, are often diagnosed later in childhood because of developmental delay or seizures. Patients with intermittent MSUD have a normal childhood development, grow normally and develop a normal intelligence. Physiologically, they have normal laboratory values including branched-chain amino acid levels, but under stressful situations, such as infection or surgery, they can suffer acute metabolic decompensation. Thiamin-responsive and dihydrolipoyl dehydrogenase (E3)-deficient MSUD are both very rare and represent more complex clinical entities. MSUD is one of the few examples of the successful implementation of population-wide newborn screening to detect inherited metabolic disease. The widely used Guthrie test, legally required in 20 countries and also in

most states of the US, is based on the observation that the growth of *Bacillus subtilis* is inhibited by 4-azaleucine under culture conditions with nutrient-depleted medium. This growth inhibition is reversed by the high leucine levels in the blood spot from a newborn with MSUD. The test detects only children with classic MSUD, the intermediate form and E3 deficiency, but generally not those with the intermittent or thiamin-responsive forms of MSUD.

The life-threatening sequelae of MSUD can be largely prevented when treatment is initiated immediately following a positive test. Therapy options include rapid removal of toxic metabolites (i.e. by haemodiafiltration), reversal of the patient's catabolism (insulin replacement and high-carbohydrate diet) and nutritional support, including branched-chain amino acid-free formulas. These principals also apply to patients with pancreatitis due to MSUD [22]. Once the acute episode of clinical deterioration in an MSUD patient has been controlled, the long-term treatment includes a diet with restricted intake of branched-chain amino acids and/or supplementation of thiamin at pharmacological doses. It needs to be remembered that diagnostic branched-chain amino acid levels in patients with intermittent MSUD are detected only during acute episodes and that these acute attacks are often exacerbated by infections, operations or trauma. Although not applicable in most patients, orthotopic liver transplantation is a new treatment option with which this metabolic disorder can be fully corrected.

Homocystinuria Due to Cystathionine β-Synthase Deficiency

Cystathionine β-synthase (CBS) deficiency is a disorder of methionine degradation inherited in an autosomal recessive manner that has been reported from all regions of the world with an estimated prevalence of between 1/20,000 and 1/1,000,000. The disease entity was initially reported in the early 1960s as homocystinuria and the enzymatic defect was later found to affect CBS. In terms of the underlying genetic alterations, a considerable heterogeneity appears to be present in different CBS-deficient families. The CBS gene was identified on chromosome 21q22.3 and more than 100 different disease-causing mutations have been identified so far. CBS is the key enzyme in the metabolism of methionine. Because of insufficient activity of CBS, there is an accumulation of homocysteine (an intermediate metabolite in the degradation of methionine) in the plasma of affected individuals (20- to 50-fold increase). Affected patients reveal a depletion of cysteine resulting in various biochemical abnormalities including the metabolism of glutathione.

A variety of clinical signs and symptoms have been reported to affect patients with homocystinuria caused by CBS deficiency. They predominantly involve the patients' eyes (e.g. luxation or subluxation of the lens, myopia, retinal abnormalities), skeletal bones (osteoporosis, scoliosis, marfanoid stature), vascular system (recurrent and often severe thromboembolism, livedo reticularis) and central nervous system (mental retardation, psychiatric abnormalities, seizures). Other, less frequently found signs are thin and brittle skin, endocrine abnormalities and myopathy.

The major cause of morbidity and mortality in patients with CBS deficiency remain the thromboembolic events that can affect the vessels of any organ system including the brain, the coronary arteries and pulmonary and peripheral arteries. On postmortem histology of CBS-deficient patients, almost every large- or medium-sized artery may be affected by marked fibrous thickening of the intima and frayed and split muscle and elastic fibers of the media. Lipid deposition is usually absent. The pancreatitis of patients with CBS deficiency [24–26] could therefore correspond to the known vascularly induced varieties of the disease. However, disturbance of glutathione metabolism might be another explanation for the increased risk of pancreatitis. About 50% of patients with CBS deficiency respond to treatment with pharmacological doses of pyridoxine, the co-factor of CBS, in combination with folic acid with a decrease or complete normalization of homocysteine, methionine and cysteine plasma levels. B6-nonresponders have to be treated with a strict diet reduced in methionine and supplemented with cystine and betaine – the latter supporting remethylation of homocysteine.

3-Hydroxy-3-Methylglutaryl-CoA Lyase Deficiency

Pancreatitis has been repeatedly seen in organic aciduria due to impaired degradation of leucine. One of these rare disorders is 3-hydroxy-3-methylglutaric aciduria, which is most commonly found in patients of Arabic parentage. It is inherited in an autosomal recessive manner and thought to represent a monogenic disease. It was first reported in 1976 and its symptom onset typically begins either in the first days of life or later in infancy and childhood. Some patients remain asymptomatic throughout

their lifetime. Patients present with metabolic acidosis and hypoglycaemia which can be characteristically associated with vomiting, hypotonia and lethargy progressing to coma. The biochemical parameters may resemble Reye's syndrome. In metabolic acidosis, children typically do not develop ketosis because 3-hydroxy-3-methylglutaryl-CoA lyase activity is deficient and would be required for ketone formation. Half of the patients have hepatomegaly and elevated transaminases. The cause of pancreatitis in patients with 3-hydroxy-3-methylglutaryl-CoA lyase deficiency is not known [27, 28], but its onset may be related to either acidosis or hypoglycaemia. Psychomotor retardation is common and probably secondary to severe or recurrent hypoglycaemia. Diagnosis is confirmed by detecting a characteristic profile of organic acids of leucine catabolism in the urine (increase in urinary 3-hydroxy-3-methylglutaric acid, 3-methylglutaconic acid, 3-hydroxyisovaleric acid or 3-methylglutaric acid). Treatment during acute episodes of hypoglycaemia consists of glucose infusions and the correction of acidosis. Patients are then fed a diet low in fat and leucine together with a high-carbohydrate diet. Patients should avoid extended fasting because of the associated hypoglycaemia and fatty acid oxidation. During infection or following immunization, on the other hand, an increased protein catabolism results in elevated leucine metabolism. Under both conditions, a catabolic state must be avoided or aggressively treated. It should be mentioned that 3-hydroxy-3-methylglutaryl-CoA lyase deficiency is but one example of inborn errors of branched-chain amino acid metabolism (examples of other organoacidurias are methylmalonaciduria and propionaciduria) that can be associated with pancreatitis.

Acute Intermittent Porphyria

Porphyrias are inherited or acquired disorders that affect specific enzymes required for the biosynthesis of haeme, the critical component of haemoglobin, and lead to accumulation of porphyrin and porphyrin precursors. Acute intermittent porphyria is an autosomal dominant disorder which is caused by a relative deficiency of the enzyme porphobilinogen deaminase [porphobilinogen ammonia-lyase (polymerizing) (EC 4.3.1.8)]. Affected patients have only 50% of porphobilinogen deaminase activity compared to wild-type relatives. Most affected carriers of porphobilinogen deaminase mutations never develop the disease phenotype throughout their lives, and acute episodes of porphyria are usually triggered exogenously by fasting, stress, steroid hormones and a multitude of pharmaceutical agents and drugs which induce hepatic microsomal cytochrome P-450 and delta-aminolevulinic acid synthase. The incidence varies between different parts of the world (5–10/100,000 for the mutation, 1–2/100,000 for the disease phenotype) but is highest among northern Europeans. If symptoms develop, they usually begin after puberty and more frequently affect women than men. The most prominent clinical symptoms involve the peripheral, autonomic or central nervous system and result in neuropathy with a plethora of symptoms. The great clinical variety of porphyria-associated neurological and central nervous system symptoms is, unfortunately, still responsible for the fact that the prevalence among psychiatric patients remains higher than in the general population. Another leading clinical symptom during acute episodes of intermittent porphyria is severe abdominal pain, which can involve nausea and vomiting, diarrhoea and constipation, ileus, back pain and renal and hepatic dysfunction. Although episodes of acute pancreatitis associated with acute intermittent porphyria have been reported [29–33], they represent less a pathophysiological dilemma than an important differential diagnosis. The symptoms of both diseases can overlap to a significant extent and distinguishing between them is important because it has therapeutic consequences. The diagnosis of acute intermittent pophyria is commonly made by demonstrating increased porphobilinogen, porphyrin and delta-aminolevulinic acid levels in the patient's urine, which, in 50% of cases, has a red or brownish colour. Therapy for an acute episode is initially symptomatic, with glucose or fructose infusions, induced diuresis and, failing that, infusion of haemearginate, which suppresses delta-aminolevulinic acid synthase in the liver.

The human gene for porphobilinogen deaminase is located on chromosome 11q23 and contains 15 exons spread over 10 kb of DNA. Ten different mutations have so far been reported and have been grouped into four subclasses of structural changes. Two different enzyme isoforms are expressed, respectively, in erythrocytes and the liver. Molecular diagnosis is not usually required unless predictive testing for at-risk relatives is specifically asked for and should generally be discouraged for asymptomatic subjects. The critical advice for affected patients is to avoid stress, alcohol and catabolic situations. Patients are regularly given a booklet of pharmaceutical agents with known porphyria-inducing potential, as can be found in almost every national drug formulary.

Pyruvate Kinase Deficiency

Because erythrocytes have no mitochondria, they rely entirely on anaerobic glycolysis for energy generation. One of the critical enzymes involved in anaerobic glycolysis is pyruvate kinase. Pyruvate kinase deficiency is the most common erythrocyte enzymopathy and an autosomal recessive disorder. Therefore, only homozygote and compound heterozygote carriers are clinically affected. Mutant alleles have been found at a frequency of between 0.1 and 6% in different populations. The disease has a worldwide distribution but is most common in northern Europeans and particularly prevalent among Pennsylvania Amish. Deficiency of pyruvate kinase results in impaired glycolysis and thus in a hereditary form of lifelong chronic haemolysis of variable severity. The characteristic symptoms are recurrent chronic jaundice, mild to moderate splenomegaly and an increased incidence of gallstone disease. Symptoms usually begin in early infancy or childhood but some rare patients are diagnosed as adults. The diagnosis is made by demonstrating decreased erythrocyte pyruvate kinase activity, but an increase in the ratio of 2,3-diphosphoglycerate to ATP is already indicative of this specific enzymopathy. Because pyruvate kinase is genetically polymorphic and has a broad range of molecular heterogeneity, most affected patients are compound heterozygotes and homozygotes are rare. Pancreatitis can occur in patients with pyruvate kinase deficiency [34] and is most frequently caused by gallstones. Gallstone disease is very common in this group of patients and can develop as early as infancy.

Cystinuria

Cystinuria is a rare inborn error of metabolism, and renal stones composed of cystine crystals were recognized as a disease entity in the 19th century. Cystinuria has a worldwide distribution with an incidence of between 1 and 10/100,000 but is found more frequently among north African Jews. Cystinuria is transmitted as an autosomal recessive trait. The underlying mechanism is defective amino acid transport for the dibasic amino acids cystine, lysine, arginine and ornithine, which mainly involves the epithelial cells of the kidneys and the gastrointestinal tract. The gene for the human sodium-independent transporter of cystine and dibasic amino acids (SLC3A1, or previously rBAT) encodes a protein of 680 amino acids and is located on chromosome 2q16–21. More than 10 mutations and polymorphisms in different portions of the protein have been reported from unrelated kindreds. The predominant clinical feature of patients with cystinuria is the formation of radio-opaque cystine stones in the urinary tract. Most patients are diagnosed with calculous kidney or urinary tract disease in their twenties or thirties, but some patients can be children or already in their eighties when they first develop symptoms. Often, the correct diagnosis in a patient with urinary calculi can be made by simple microscopy of the sediment of morning urine and the demonstration of the characteristic hexagonal cystine crystals. Acidification of the urine specimen precipitates cystine crystals and makes them easier to detect, and a cyanide-nitroprusside test has been widely applied as a chemical screening procedure. More sophisticated techniques include thin-layer chromatography, high-voltage electrophoresis, column amino acid analysis, liquid chromatography and mass spectrometry to identify cystine and dibasic amino acids.

Urinary tract stones generally develop when the cystine excretion rate exceeds 300 mg/g of creatinine in acid urine, and therapy is therefore directed at reducing cystine uptake and increasing cystine solubility in the urine. This can be achieved by alkalinizing the patient's urine above pH 7.5 and diluting it by high oral fluid intake. If these measures are insufficient to prevent stone formation, treatment with *D*-penicillamine, N-acetyl-*D*-penicillamine or mercaptopropionylglycine is considered, but troubling side effects including hypersensitivities, skin disorders and epidermolysis must be anticipated. Angiotensin-converting enzyme inhibitors (i.e. captopril) have therapeutic potential that needs to be further evaluated in clinical trials. Patients with cystinuria are susceptible to all complications of urinary stone disease including painful colics, recurrent infection and chronic renal failure. They often require interventional removal of their calculi by lithotripsy or open surgery and a significant number of them become transplant recipients. Cystinuria has been associated with a variety of other disorders, including familial pancreatitis [35]. It is not clear whether this association is caused by co-transmission of one of the recently identified trypsinogen mutations that characterize hereditary pancreatitis, might indicate a de novo formation of pancreatic duct calculi in cystinuria or is based on the known association between chronic renal failure and pancreatic disease [36, 37].

Lysinuric Protein Intolerance and Other Cationic Aminoacidurias

Lysinuric protein intolerance is a rare autosomal recessive disorder that was first described in 1965. By far the highest incidence (1/60,000) is found among the Laplander population of Finland. The disease is characterized by postprandial hyperammonaemia caused by a primary defect in the transport of the cationic amino acids lysine, arginine and ornithine in the epithelial cells of the kidneys and gastrointestinal tract and secondarily by a disturbance of the urea cycle. Lysinuric protein intolerance has been found to be caused by mutations in the amino acid transporter gene SLC7A7, located on chromosome 14q.

Because of the increased urinary excretion and decreased intestinal absorption of cationic amino acids in general and of the essential amino acid lysine in particular, the bodies of patients with lysinuric protein intolerance are progressively depleted of these amino acids. Deficiency of ornithine subsequently leads to an impairment of the urea cycle. Affected patients experience periods of hyperammonaemia and accordingly develop nausea and vomiting and avoid protein-rich foods. Newborns and infants after the breast-feeding period fail to thrive, and symptoms of protein malnutrition are further aggravated by lysine deficiency. Subsequently, patients develop hepatosplenomegaly, osteoporosis and bone fractures, sparse hair, muscle hypotonia, anaemia and coagulopathies and pulmonary, renal and sometimes central nervous system disorders.

In patients with lysinuric protein intolerance, the plasma concentration of cationic amino acids in plasma is low and the concentrations of glutamine, alanine, serine, proline, citrulline and glycine may be elevated. The urinary excretion of lysine is excessive and that of arginine and ornithine is also elevated. Serum ammonia increases after protein-containing meals but is normal under fasting conditions. Patients with lysinuric protein intolerance are treated with a protein-restricted and citrulline-supplemented diet and usually respond with an improvement of symptoms, although the aversion to dietary proteins remains. Patients with lysinuric protein intolerance-associated pulmonary disease, but not with renal complications, have been reported to respond to steroids.

Several cases of pancreatitis have been reported in patients with lysinuric protein intolerance, and the morphologic alterations in the pancreas can include inflammatory changes, necrosis, intraductal protein plugs, atrophy and fibrosis [38, 39]. The underlying defect is thought to be the severe protein deficiency, because similar pancreatic changes have been found in patients with kwashiorkor. In at least one kindred that was previously classified as having familial pancreatitis [39], the underlying cause may have been either primary lysinuric protein intolerance or co-inheritance of lysinuric protein intolerance together with one of the other gene mutations that predispose to familial pancreatitis and are discussed elsewhere in this volume.

Conclusions

Most of the inborn errors of metabolism reviewed above are rare disorders. For a complete and extensive overview of their genetics, biochemistry and clinical treatment, the reader is referred to the latest edition of the authoritative textbook of Scriver et al. [40]. In many of these diseases, pancreatitis is neither common nor is its pathogenesis well understood. Because many of these disorders 'run in families' from regions of the world where consanguineous marriages are common, they should be kept in mind – and sometimes need to be ruled out – when patients with hereditary pancreatitis present with unusual clinical symptoms and signs. Particularly the organic acidurias and inherited hyperlipidaemias should be considered as a possible cause of recurrent pancreatitis.

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