The Metabolic & Molecular Bases of Inherited Disease

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CHAPTER 192

Lysinuric Protein Intolerance and Other Cationic Aminoacidurias

Olli Simell

1. Membrane transport of cationic amino acids lysine, arginine, and ornithine is abnormal in four disease entities: classic cystinuria; lysinuric protein intolerance (hyperdibasic aminoaciduria type 2, or familial protein intolerance); hyperdibasic aminoaciduria type 1; and isolated lysinuria (lysine malabsorption syndrome). Cystinuria, the most common of these, is dealt with in Chap. 191. About 100 patients with lysinuric protein intolerance (LPI) have been reported or are known to me. Almost half of them are from Finland, where the prevalence of this autosomal recessive disease is 1 in 60,000. Autosomal dominant hyperdibasic aminoaciduria type 1 has been described in 13 of 33 members in a French Canadian pedigree, and isolated lysinuria has been described in one Japanese patient.

   Arginine and ornithine are intermediates in the urea cycle; lysine is an essential amino acid. In lysinuric protein intolerance (LPI) (MIM 222700), urinary excretion and clearance of all cationic amino acids, especially of lysine, are increased, and these amino acids are poorly absorbed from the intestine. Their plasma concentrations are low, and their body pools become depleted. The patients have periods of hyperammonemia caused by "functional" deficiency of ornithine, which provides the carbon skeleton of the urea cycle. Consequently, nausea and vomiting occur, and aversion to protein-rich food develops. The patients fail to thrive, and symptoms of protein malnutrition are further aggravated by lysine deficiency.
2. Patients with LPI are usually symptom-free when breast-fed but have vomiting and diarrhea after weaning. The appetite is poor, they fail to thrive, and if force-fed high-protein milk or formulas, they may go into coma. After infancy, they reject high-protein foods, grow poorly, and have enlarged liver and spleen, muscle hypotonia, and sparse hair. Osteoporosis is prominent, and fractures are not uncommon; bone age is delayed. The mental prognosis varies from normal development to moderate retardation; most patients are normal. Four patients have had psychotic periods. The final height in treated patients has been slightly subnormal or low-normal. Pregnancies are risky: Profound anemia develops, platelet count decreases, and severe hemorrhages during labor and a toxemic crisis have occurred, but the offspring are normal if not damaged by delivery-related complications. Acute exacerbations of hyperammonemia have not been a frequent problem in treated patients, but may have been the cause of the sudden death in one adult male after moderate alcohol ingestion. About two thirds of the patients have interstitial changes in chest radiographs. Some patients have developed acute or chronic respiratory insufficiency, which in a few has led to fatal pulmonary alveolar proteinosis and to multiple organ dysfunction syndrome. Patients present with fatigue, cough, dyspnea during exercise, fever, and, rarely, hemoptysis, and may also show signs of nephritis and renal insufficiency. One adult patient with pulmonary symptoms has been treated with high-dose prednisolone and is in remission over 6 years after the occurrence of the symptoms. In another patient, bronchoalveolar lavages have produced immediate relief during several subacute exacerbations.
3. In LPI, the concentrations of the cationic amino acids in plasma are subnormal or low-normal, and the amounts of glutamine, alanine, serine, proline, citrulline, and glycine are increased. Lysine is excreted in urine in massive excess, and arginine and ornithine in moderate excess. Daily urine contains a mean amount of 4.13 mmol lysine (range 1.02 to 7.00), 0.36 mmol arginine (0.08 to 0.69) and 0.11 mmol ornithine (0.09 to 0.13) per 1.73 m^2 body surface area. The mean renal clearances are 25.7, 11.5, and 3.3 ml/min/1.73 m^2, respectively; occasional values suggest net tubular secretion of lysine. Cystine excretion may be slightly increased. Blood ammonia and urinary orotic acid excretion are normal during fasting but are increased after protein meals. The serum urea level is low to normal, and lactate dehydrogenase, ferritin, and thyroid-binding globulin levels are elevated.
4. The transport abnormality is expressed in the kidney tubules, intestine, cultured fibroblasts, and probably in the hepatocytes, but not in mature erythrocytes. In vivo and in vitro studies of the handling of cationic amino acids in the intestine and kidney strongly suggest that the transport defect is localized at the basolateral (antiluminal) membrane of the epithelial cells. In vivo, plasma concentrations increase poorly after oral loading with the cationic amino acids, but also if lysine is given as a lysine-containing dipeptide. Dipeptides and other oligopeptides use a different transport mechanism not shared with that of free amino acids. The dipeptide thus crosses the luminal membrane normally, and is hydrolyzed to free amino acids in the cytoplasm of the enterocyte. An efflux defect at the basolateral membrane explains why the dipeptide-derived

A list of standard abbreviations is located immediately preceding the index in each volume. Additional abbreviations used in this chapter include: HHH = hyperornithinemia-hyperammonemia-homocitrullinuria; LDH = lactate dehydrogenase;

fluxes of lysine in intestinal biopsy specimens have confirmed that the defect indeed localizes to the basolateral cell surface. Similar cellular localization of the defect in the kidney tubules is suggested by infusions of citrulline, which cause not only citrullinuria but also significant argininuria and ornithinuria. Because citrulline and the cationic amino acids do not share transport mechanisms in the tubules, part of the citrulline is converted to arginine and then to ornithine in the tubule cells during reabsorption. A basolateral transport defect prohibits antiluminal efflux of arginine and ornithine, which accumulate and escape through the luminal membrane into the urine. The genetic mutations in LPI and possibly in all cationic aminoaciduria apparently lead to kinetic abnormalities in the transport protein(s) of the cationic amino acids. This is suggested by the fact that increasing the tubular load of a single cationic amino acid by intravenous infusion increases its tubular reabsorption, but reabsorption remains subnormal even at high loads. he other cationic amino acids are able to compete for the same transport site(s) also in LPI, but an increase in the load of one cationic amino acid frequently leads to net secretion of the others.

The plasma membrane of cultured fibroblasts shows a defect in the trans-stimulated efflux of the cationic amino acids; i.e., their flux out of the cell is not stimulated by cationic amino acids present on the outside of the cell as efficiently as it is in the control fibroblasts. The percent of trans-stimulation of homoarginine efflux in the fibroblasts of the heterozygotes is midway between that of the patients and the control subjects.

5. The exact cause of hyperammonemia in LPI remains unknown. The enzymes of the urea cycle have normal activities in the liver, and the brisk excretion of orotic acid during hyperammonemia supports the view that N-acetylglutamate and carbamyl phosphate are formed in sufficient quantities. Low plasma concentrations of arginine and ornithine suggest that the malfunctioning of the cycle is caused by a deficiency of intramitochondrial ornithine. This hypothesis is supported by experiments in which hyperammonemia after protein or amino nitrogen loading is prevented by intravenous infusion of arginine or ornithine. Citrulline, a third urea cycle intermediate, also abolishes hyperammonemia if given orally, because, as a neutral amino acid, it is well-absorbed from the intestine. Ornithine deficiency in LPI has recently been questioned because cationic amino acids and their nonmetabolized analogues accumulate in higher-than-normal amounts in intestinal biopsy specimens and cultured fibroblasts from LPI patients in vitro and the concentrations of the cationic amino acids in liver biopsy samples are similar or higher in the patients when compared to these concentrations in the control subjects. If hyperammonemia is not due to simple deficiency of ornithine, it could be caused by inhibition of the urea cycle enzymes by the intracellularly accumulated lysine; by a coexisting defect in the mitochondrial ornithine transport necessary for the function of the urea cycle; or by actual deficiency of ornithine in the cytoplasm caused by abnormal pooling of the cationic amino acids into some cell organelle(s), most likely lysosomes. The latter two explanations imply that the transport defect is expressed also in the organelle(s).
6. Lysine is present in practically all proteins, including collagen. Lysine deficiency may cause many of the features of the disease that are not corrected by prevention of hyperammonemia, including enlargement of the liver and spleen, poor growth and delayed bone age, and osteoporosis. Oral lysine supplements are poorly tolerated by the patients because of their poor intestinal absorption. ε-*N*-acetyl-L-lysine, but not homocitrulline, efficiently increases plasma concentration of lysine in the patients, but acetyllysine or other neutral lysine analogues have not been used for supplementation.
7. Recently, a 622-amino-acid retroviral receptor (murine leukemia viral receptor REC1) with 12 to 14 potential membrane-spanning domains has been cloned. The physiological role of the receptor was soon found to be that of a cationic amino acid transporter at the cell membrane; the protein was hence renamed MCAT-1, mouse cationic amino acid transporter-1. The functional characteristics of the transporter are similar to those of system y^+, a widely expressed Na^+-independent transport system for cationic amino acids. The human counterpart of the mouse REC1 gene, encoding the retroviral receptor-transport protein, has been assigned to chromosome 13q12-q14 and named ATRC1. MCAT-1 (and y^+) activity is not expressed in rodent liver, but two other related cationic amino acid transport proteins, formed presumably as a result of alternative splicing — Tea (T cell early activation; expressed also in activated T and B lymphocytes) and MCAT-2 — are probably responsible for the low-affinity transport of cationic amino acids that is characteristic of (mouse) liver. Studies addressing the ATRC1 gene as well as the Tea and MCAT-2 genes as candidate genes for LPI are under way.
8. Treatment in lysinuric protein intolerance consists of protein restriction and supplementation with oral citrulline, 3 to 8 g daily during meals. Patients are encouraged to increase their protein intake modestly during citrulline supplementation, but aversion to protein in most patients effectively inhibits them from accepting more than the minimal requirement. The treatment clearly improves the growth and well-being of the patients. Pulmonary complications (interstitial pneumonia, pulmonary alveolar proteinosis, cholesterol granulomas, and respiratory insufficiency) have occasionally responded to early treatment with high-dose prednisolone, or to bronchoalveolar lavages. No therapy is known for the associated renal disease and renal failure.
9. The clinical and biochemical findings in other cationic aminoacidurias differ slightly from those in lysinuric protein intolerance. The symptoms of the index case with hyperdibasic aminoaciduria type 1 resemble those of LPI, but the other affected members of the pedigree are clinically healthy. The Japanese patient with isolated lysinuria has severe growth failure, seizures, and mental retardation. Her transport defect is apparently limited to lysine, and hyperammonemia is not a feature of the disease.

Perheentupa and Visakorpi described the first three patients with "familial protein intolerance with deficient transport of basic amino acids" in 1965.[1] The disease is now called lysinuric protein intolerance (LPI) (MIM 222700) or "hyperdibasic aminoaciduria type 2."[2–5] Over 100 patients with this autosomal recessive disease have been described or are known to me; 41 of them are Finns or Finnish Lapps.[6–52] The incidence in Finland is 1 in 60,000 births but varies considerably within the country.[2,53] Patients of black and white American, Japanese, Turkish, Moroccan, Arab, Jewish, Italian, French, Dutch, Irish, Norwegian, Swedish, and Russian origin have also been described. The fascinating combination in the disease of urea cycle failure, expressed as postprandial hyperammonemia, and a defect in the transport of the cationic amino acids lysine, arginine, and ornithine in the intestine and kidney tubules has led to extensive studies of the mechanisms that link these two phenomena. The mechanisms are still partly unresolved, and the sequence of events leading to hyperammonemia is unclear. We can simplify our knowledge by

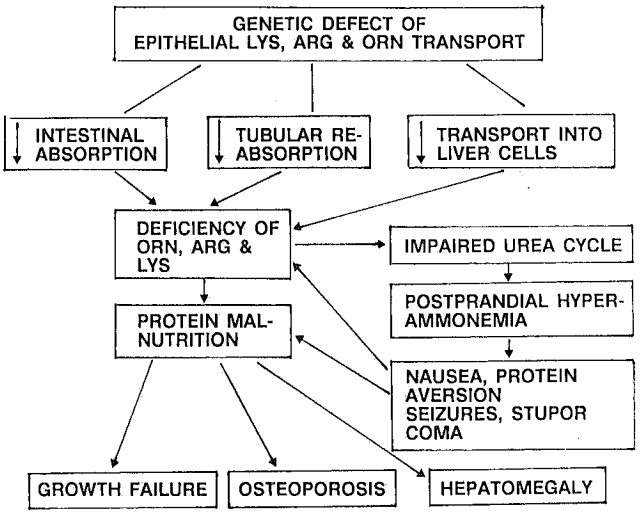

Fig. 192-1 The suggested pathogenesis of lysine, arginine, and ornithine deficiency, hyperammonemia, and aversion to protein in LPI.

saying that hyperammonemia is caused by "functional deficiency" of the urea cycle intermediates arginine and ornithine in the urea cycle[4,11,14,54] (Fig. 192-1). LPI has also been a productive model for studies of cellular transport: It is the first human disease where the transport defect has been localized to the basolateral (antiluminal) membrane of the epithelial cells.[55–57] Further, in LPI the parenchymal cells show a defect in the trans-stimulated efflux of the cationic amino acids, suggesting that the basolateral membrane of the epithelial cells and the plasma membrane of the parenchymal cells have analogous functions.[58,59]

Recently, the first candidate gene for LPI, ATRC1, encoding a human cationic amino acid transporter, has been mapped to the long arm of chromosome 13 (13q12-q14).[60] Without further proof, it is intriguing to hypothesize how a mutation in this or in a functionally similar gene or in genes encoding regulatory proteins of these transporters might lead to the membrane-selective cationic amino acid transport defect of LPI and to the complicated clinical features of the disease.

Several patients with variant forms of cationic aminoaciduria have been described in which the protein tolerance often is better than in LPI and the selectivity and severity of cationic aminoaciduria differs.[23,25,33,61,62] In the report by Whelan and Scriver[61] only the history of the index case suggested hyperammonemia, but other members of the pedigree have been symptom-free. The inheritance of this hyperdibasic aminoaciduria type 1 is autosomal dominant, implying that the patients are heterozygous for LPI or another type of hyperdibasic aminoaciduria.

CLINICAL ASPECTS

Lysinuric Protein Intolerance

Natural Course of the Disease. The gestation and delivery of infants with LPI has been uneventful.[4–6,9–11,35] Breast-fed infants usually thrive because of the low protein concentration in human milk, but symptoms of hyperammonemia may appear during the neonatal period and reflect exceptionally low protein tolerance or a high protein content in the breast milk. Nausea, vomiting, and mild diarrhea appear usually within 1 week of weaning or another increase in the protein content of the meals. Soy-based formulas are perhaps slightly better tolerated than cow's milk. The infants are poor feeders, cease to thrive, and have marked muscular hypotonia. The patient's liver and spleen are enlarged from the neonatal period onward. The association of episodes of vomiting the diagnosis frequently has been delayed until the school age or even adulthood.[35,47,63]

Around the age of 1 year, most patients begin to reject cow's milk, meat, fish, and eggs. The diet then mainly contains cereals cooked in water, potatoes, rice and vegetables, fruits and juices, bread, butter, and candies. The frequency of vomiting decreases on this diet, but accidental increases in protein intake lead to dizziness, nausea, and vomiting. A few patients have lapsed into coma, to the point where the EEG became isoelectric when the children were tube-fed with high-protein foods.[27,35,40,41,47] Enteral alimentation and total parenteral nutrition may cause symptoms in patients who have remained undiagnosed, because the protein or amino acid loads often exceed patient's tolerance. Prolonged, moderately increased protein intake may lead to dizziness, psychotic periods, chronic abdominal pains, or suspicion of abdominal emergencies.

Bone fractures occur frequently, often after minor trauma.[4,14,30,35,63–66] In a Finnish series, 20 of 29 patients (69 percent) had suffered from fractures of the long bones or of compression fractures of the lumbar spine; 10 (34 percent) had had more than 2 fractures during the 18-year follow-up.[63–65] Most fractures occurred before the age of 5 years. Symptoms of osteoarthrosis often begin at the age of 30 to 40 years. The radiologic signs of osteoporosis are usually severe before puberty but decrease with advancing age. The effect of citrulline therapy on osteoporosis is minimal.

Our accumulating experience with the late complications associated with the disease, together with recent reports of patients from outside Finland, suggest that in a sizable proportion of the patients the classic symptoms of protein intolerance may remain unnoticed. Instead, the patients may present with interstitial lung disease or respiratory insufficiency, or have renal glomerular or glomerulotubular disease with or without renal insufficiency as the first clinical finding (see "Complications and Autopsy Findings" below).

Physical Findings. Muscular hypotonia and hypotrophy are usually noticeable from early infancy but improve with advancing age.[35] Most patients are unable to perform prolonged physical exercises, but acute performance is relatively good. The body proportions of patients after the first couple of years of life are characteristic: the extremities are thin, but the front view of the body is squarelike with abundant centripetal subcutaneous fat. The hair is thin and sparse, the skin may be slightly hyperelastic, and the nails are normal. The liver is variably enlarged, and the spleen is often palpable and is large by ultrasound.

Patients who have remained undiagnosed until the age of several years have had characteristics typical of protein-calorie malnutrition and frequently resemble patients with advanced celiac disease. The subcutaneous fat may be reduced and the skin "loose" and "too large for the body" (Fig. 192-2).

The ocular fundi have been normal by ophthalmoscopy.[35] Of 20 patients studied, 14 had minute opacities in the anterior fetal Y suture of both lenses. In 10 patients, the opacities were surrounded by minute satellites. The opacities were never large enough to cause visual impairment and have remained stable, in some patients now for over 25 years. The mechanism underlying the lens abnormalities is unknown.[67]

The dentition of the patients has been normal, and the patients do not appear to be especially prone to caries, despite the high carbohydrate content of the diet.

Growth. Birth weights and lengths have been normal for gestational age, and postnatal growth is normal before weaning. The growth curves then begin to deviate progressively from the normal mean, and, at the time of diagnosis, 16 of 20 Finnish patients were more than 2 SD below the mean height, 12 patients were more than 3 SD, 6 patients more than 4 SD, 2 patients more

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