Chapter 39

Skin Diseases Due to Disorders of Amino Acid Metabolism

These skin diseases are usually the result of a congenital deficiency of enzymes which catalyze the synthesis or transport of specific amino acids. Disorders of amino acid metabolism manifest themselves in cutaneous organs as anomalies of the pigmentation of skin and hair, in structural disorders of the hair, and in some cases in pellagroid symptoms. In patients with congenital structural disorders of the hair it is important to remember disorders of amino acid metabolism and to have amino acid assays carried out on blood or urine.

Phenylketonuria [Fölling 1934]

Synonyms. Fölling's disease, phenylpyruvic oligophrenia, oligophrenia phenylpyruvica.

Definition. Inherited enzymopathy. Owing to the absence of phenylalanine hydroxylase, the hydroxylation of phenylalanine to tyrosine is blocked. This manifests itself clinically in oligophrenia, seizures, and a fair complexion.

Occurrence. It is estimated that there is 1 case per 10000 of population. Inheritance of the disease is autosomal recessive.

Pathogenesis. Owing to the absence of phenylalanine hydroxylase, phenylalanine undergoes transamination to pyruvic acid, which accumulates in the blood. There is increased excretion of phenylalanine, pyruvic acid in the urine (phenylketonuria) and a relative deficiency of tyrosine in the body.

Clinical Findings. The main site affected by the disorder is the central nervous system. The children affected show varying degrees of mental retardation due to toxic brain damage consequent upon the accumulation of phenylalanine and its metabolites, increased levels of which are also detectable in the cerebrospinal fluid.

Skin Findings. Due to the absence of hydroxylation of phenylalanine, insufficient amounts of tyrosine form. Therefore not enough of this amino acid is available for melanin synthesis. This results in the fair complexion: fair skin lacking pigment, light blond hair, and blue eyes. Pigmented nevi also seem to occur less often in these children. The fair complexion is not an invariable sign; its causal association with the enzyme defect becomes clear in that the hair darkens if tyrosine is given in the diet.

Photophobia and hyperhidrosis with a mouse-like odor are not uncommon. It is important to note that the skin of these patients is usually very dry (steato­sis with fine scaling). In some 20%-50% of cases there are symptoms of atopic eczema, particularly low-grade eczematous lesions also of the cheeks.

Diagnosis. Early diagnosis in infancy is now possible. Green coloration of the urine with 5% ferric chloride solution or positive results with Phenistix strips are diagnostically conclusive. In some cases, however, the characteristic excretion of phenylalanine metabolites is absent during the first few weeks of life. Nevertheless, a plasma phenylalanine level of 15.0 mg/100 ml or more gives a basis for suspecting the disease.

Prognosis. Poor, unless treatment is given very early.

Treatment. If started early, a diet poor in phenylalanine prevents mental retardation. Careful compliance with the diet and appropriate pediatric follow-up are required. The eczematoid skin changes respond rapidly to low-potency corticosteroids in creams. Appropriate skin care is important (baths with bath oil added, application of water-in-oil emulsions).
Hartnup Syndrome [Baron et al. 1956]

Synonyms. Hartnup disease, pellagra-cerebellar ataxia-renal aminoaciduria syndrome.

Definition. Inherited disorder leading to a defect in the cellular transport of neutral amino acids and to the dermatological and neurological symptoms with specific aminoaciduria. The term Hartnup syndrome originates from the name of the patient in whom this disease was first diagnosed in 1951.

Occurrence. Rare, probably autosomal recessive inheritance, multiple alleles.

Pathogenesis. The skin changes suggest a deficiency of nicotinic acid amide. It is possible to alleviate the neurological and dermatological symptoms by the administration of nicotinic acid. It may be that there is a reduced absorption of tryptophan from the intestine so that there is a deficiency of this amino acid for the synthesis of nicotinic acid. The biosynthesis of nicotinic acid amide itself may be blocked due to a genetic defect in cells of the skin, brain, and even intestine and kidneys. The possibility of an increased formation of indole derivatives due to increased levels of tryptophan in the intestinal lumen by bacterial fermentation has also been proposed; these derivatives might in turn inhibit the biosynthesis of nicotinic acid amide. In any event, the increased excretion of tryptophan indole bodies (indolylacrylic acid) and other amino acids in the urine is striking. There is a specific malabsorption of tryptophan and perhaps some other amino acids such as alanine, serine, glycine, and phenylalanine due to a defect in the mechanism of transport of these amino acids through the mucosa of the jejunum. This is likely responsible for the intracellular deficiency of nicotinic acid amide. A similar defect in the renal reabsorption mechanism could be responsible for the aminoaciduria.

Clinical Findings. The primary signs are paroxysmal cerebellar ataxia with nystagmus and diplopia, attacks of migraine, gradual inhibition of mental development, and skin manifestations.

Skin Findings. These are seasonal and appear as photosensitivity with changes only in the areas of the skin exposed to light (face, nose, and backs of the hands and also knees in children), especially in the spring. The changes sometimes present a more pellagroid picture or correspond to those of acute or subacute solar dermatitis with erythema, slight swelling, and pruritus. Sometimes, premature graying of the hair can occur.

Stomatitis, glossitis, and diarrhea have also been reported.

Urine. The chromatographic evidence of aminoaciduria is essential for the diagnosis. Many neutral amino acids are excreted in the urine in large amounts, especially those with monoaminomonocarboxylic groups. The elimination of proline, hydroxyproline, or glycine is normal. There is usually distinct indicanuria (Millon’s test positive).

Course. The condition tends to improve, if at all, with age. The dermatological and neurological symptoms may develop simultaneously or independently of each other. One common feature is their seasonal nature.

Differential Diagnosis. The disease manifests itself only in areas of skin exposed to sunlight. Pellagra or pellagroid disorders must be considered and, in addition, drug-induced phototoxic or photoallergic reactions and light-induced atopic eczema. Congenital poikiloderma and the quasi-senile (progeria-like) Cockayne’s syndrome, which is already present in the first year of life and is associated with physical and mental developmental disorders, must also be considered.

TREATMENT. High doses of nicotinic acid amide (300–600 mg daily) bring about immediate regression of the skin symptoms although normalization of the neurological disorders is only slowly achieved. It is important to avoid exposure to intense sunlight, to supply a diet that is rich enough in calories and protein, and to provide external protection from sunlight.

Alkaptonuria with Ochronosis [Virchow 1866]

Synonyms. Alkaptonuria, ochronosis.

Definition. Very rare disease which is characterized by dark pigmentation of the skin (ochronosis), arthritis, dark-colored urine, and deposits of homogentisic acid in the tissues due to a genetic disorder of tyrosine metabolism.


Pathogenesis. Owing to a genetic defect there is a deficiency of homogentisic acid oxidase. Therefore, the degradation of tyrosine remains at the stage of homogentisic acid (2,5-dioxyphenyl acetic acid). This acid accumulates especially in fibrous and cartilaginous tissues and leads to brown or more blue-black pigmentation. The blackening of the cartilage is considered to originate from the deposition of pigmented polymers that have been formed by the oxidation of homogentisic acid via benzoquinone acetic acid.

Clinical Findings. It is important to observe the triad of symptoms: dyschromia of portions of the light-exposed skin, joint symptoms, and melanuria.

Skin Findings. Owing to the deposition of homogentisic acid in cartilaginous tissues and the black pigmen-