Tyrosinemia with plantar and palmar keratosis and keratitis

An 11½-year-old boy, born of a consanguineous marriage, had mental retardation, painful plantar and palmar keratosis, and dendritic keratitis associated with tyrosinemia, p-hydroxyphenylpyruvicaciduria, p-hydroxylaceticaciduria, and p-hydroxyphenylaceticaciduria. Liver and renal functions were within normal ranges, and vitamin C loading did not correct the metabolic abnormalities. Maintenance on a low-tyrosine, low-phenylalanine diet was associated with resolution of the epithelial lesions and a decrease in the metabolic abnormalities. Four other patients with similar metabolic abnormalities may have had this clinical syndrome.

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A MENTALLY retarded boy with palmar and plantar keratosis and keratitis, the Richner-Hanhart syndrome (RHS), had phenolic aciduria and tyrosinemia in the absence of scurvy, cirrhosis, or renal tubular dysfunction. Treatment with a low phenylalanine-tyrosine diet was associated with clearing of the eye and skin lesions and the amelioration of the metabolic abnormalities. During dietary relaxation, the epithelial lesions recurred. In retrospect, four other patients with similar metabolic abnormalities[1-6] have had similar clinical features. Furthermore, the clinical features are compatible with RHS, a disorder without published biochemical findings. This report includes our clinical and biochemical findings and electron microscopic studies of the skin and eye lesions in this unusual syndrome.

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Abbreviations used
PHPLA: parahydroxyphenyllactic acid
PHPAA: parahydroxyphenylacetic acid
OHPAA: orthohydroxyphenylacetic acid
PHPPA: parahydroxyphenylpyruvic acid

CASE REPORT

The patient was the second of three children born of a marriage of first cousins. His parents were born in the province of Abruzzi, Italy, in a town with a population of less than 100 people.

Birth was normal after a 41 week gestation. Birth weight was 7 pounds, 12 ounces. The neonatal course was uneventful. Developmental milestones were slightly delayed; he sat at age 8 months, walked with support at 15 months, and walked alone at 22 months.

At 17 months of age he sustained a linear skull fracture of the left temporal bone during a fall. The fracture healed normally. Over the next 1½ years his gait was noticed to be unsteady and stiff. He was psychologically tested at age 3½ years and was considered to be moderately retarded, although a reliable score was not possible. At age 4¹¹⁄₁₂ years he was found to be functioning at the 2 year level according to the Stanford-Binet Test, Form L-M.

He was seen at the Children's Hospital Medical Center at 11½ years of age because of hyperactivity and abnormal behavior. On examination he was slender, dull appearing, and had a bird-like facies. Weight was 28.9 Kg., height 140.5 cm., and head circumference 51.5 cm. He nervously bit his nails, picked at the hyperkeratotic lesions on his palms and soles, and chewed the crusts off some of the lesions of his fingers. He had severe tics with intermittent grimacing, bizarre extension of the neck, blinking, and occasional sudden extensor movements of the right arm which seemed to occur more frequently when he appeared nervous. His gait was abnormal and accentuated by mild trundling and planting of the toes in mild valgus position. Muscular development was poor and very little subcutaneous tissue was noted. No enlargement of the liver, spleen, or thyroid was noted. The electroencephalogram was abnormal with frequent bursts of moderate- to high-voltage rhythmic delta waves lasting 1 to 10 seconds, maximal in the anterior quadrants. Several drugs were tried without beneficial results, and administration of haloperidol (Haldol) resulted in the development of extrapyramidal signs which were reversed on withdrawal of the drug.

Skin lesions. At the age of 6 years he had onset of painful, nonpruritic lesions on the feet and palms which at times spontaneously cleared. Clearing or worsening of the lesions was not related to time of the year, intercurrent illness, or topical therapy. Palmar and plantar lesions localized to the peripheral pressure-bearing areas were present. The lesions were discrete hyperkeratotic papules up to 2 cm. in diameter with irregular polycyclic borders. The palms were hyperhidrotic. There were greyish, uniformly hyperkeratotic, slightly raised plaques in the prepatellar regions and over the elbows. The nails and hair were normal. He was deeply and evenly tanned and darker than his siblings or parents, even in winter months.

Eye lesions. Since the age of 8 years, the patient had redness, excessive tearing, and photophobia of both eyes which were less severe during the summer. Abnormalities were limited to the conjunctiva and cornea. The conjunctiva was thickened and less transparent than normal and appeared as if it were constructed of an artificial membrane. In each cornea, there was a lesion made of fine lines in the branched pattern of a miniature dendrite. These lines were limited to the epithelium and occupied all but the most superficial levels of the epithelium. The major lesions occupied an inferior, paracentral location in each cornea, and in the left eye there was an additional smaller lesion with a stellate pattern a little further from the center. During a year of observation there was no change in the shape of the lesions. There was no fluorescein staining, and viral cultures of both eyes were negative. The patient's vision was 20/25 in each eye uncorrected. Applanation tension, ocular motility, field examination, anterior chambers, irides and their reactions, lenses, and fundi were not abnormal.

METABOLIC STUDIES

Tyrosinuria, tyrosyluria, and tyrosinemia were discovered during the work-up for hyperactivity at age 11½ years; they were not corrected with vitamin C loading, 500 mg. per day for two weeks. Liver and renal function studies were normal. Further studies were postponed for ten months because of an intervening trip to Italy. Upon return, the biochemical abnormalities were reconfirmed on repeat study. The skin and eye lesions were still unchanged.

Significant reduction in the degree of the biochemical derangement in tyrosine metabolism was achieved with a relatively mild and well-tolerated diet. The diet was changed from 4 to 2 Gm. of protein per kilogram per day, and from approximately 200 mg. per kilogram per day of phenylalanine and a like amount of tyrosine to approximately 60 to 90 mg. of each per kilogram per day. No meats, fish, poultry, egg whites, cheese, jello, or milk were included, and a milk substitute, 3200 AB (Mead Johnson), an investigational

preparation low in phenylalanine and tyrosine, was used to augment his protein needs. Two and one half weeks after this modest dietary reduction of phenylalanine and tyrosine, the skin and eye symptoms and lesions disappeared and his disposition improved. The skin lesions recurred within two weeks when the diet was liberalized.

There are two other children in this family. The older child, a girl, is clinically normal, and a younger brother is mildly retarded and has right exotropia and mild amblyopia. The parents and siblings have normal skin and corneas and did not exhibit any biochemical evidence of disturbed tyrosine metabolism under normal dietary conditions.

BIOCHEMICAL STUDIES

Whole blood for amino acid determinations was collected in EDTA after an overnight fast. The plasma was separated and deproteinized with solid sulfosalicylic acid and stored at −20° C. until analysis. Urine was kept frozen until analysis. Deproteinization of urine was carried out with solid sulfosalicylic acid prior to analysis. Amino acids were quantitatively determined by a modification of the Piez-Morris method using a Technicon amino acid analyzer.[7] Urinary amino acids were also examined semiquantitatively by a two-dimensional separation (high-voltage paper electrophoresis followed by chromatography with butanol-acetic acid-water).[8]

Total tyrosine and tyrosyl compounds in urine were quantitated on 24 hour urine samples by a modified Millon reaction.[9]

Parahydroxyphenyllactic acid (PHPLA) and parahydroxyphenylacetic acid (PHPAA) levels were determined on unfractionated urine by comparison with standard compounds run in parallel and separated by ascending paper chromatography (Whatman 3MM) in butanol-acetic acid-water and benzene-acetic acid-water (125:72:3) for three hours.[10]

Descending chromatography in butanol-ethanol-ammonia (4:1:1) was used to determine orthohydroxyphenylacetic acid (OHPAA).[10] Urine for OHPAA analysis was first acidified, extracted with ethylacetate, alkalinized with sodium bicarbonate, and then re-extracted with ethylacetate. An aliquot of the ethylacetate extract was chromatographed. The enzymatic spectrophotometric modification of the enol-borate method of Knox and Pitt[11] was used for parahydroxyphenylpyruvic acid (PHPPA) analysis in serum. Catalase and L-amino oxidase were omitted and the serum was deproteinized with $HClO_4$ and neutralized with potassium carbonate before use. Recovery of PHPPA added to serum was 92 per cent.

Urine PHPPA was measured by two methods: (1) modification of the enol-borate method[12] (acidification to pH 1, extraction with peroxide free ether, addition of sodium phosphate buffer, evaporation under cool air, readjustment of volume and pH to 6.5),* and (2) conversion to the 2,4-dinitrophenylhydrazone followed by separation by thin layer chromatography (silica gel) in butanol-acetic acid-water. The latter was run in parallel with a standard, eluted with glacial acetic acid, and absorption was spectrophotometrically determined at 370 nm.[10]

Homogentisic acid,[10] homovanillic acid,[10] dihydroxyphenylalanine,[13] dihydroxyphenylacetic acid,[10] δ-amino levulinic acid,[13] and porphobilinogen[14] were determined in 0.1 ml. of urine by paper chromatography.

BIOPSY STUDIES

The conjunctiva of the right eye was biopsied, and light microscopy demonstrated thickened epithilium and stroma, vacuoles in the epithelium, and an infiltration of plasma cells between the epithelium and stroma. Electron microscopic studies demonstrated many intracytoplasmic vacuoles, intranuclear electron dense particles (possibly clumping of nuclear chromatin), and nonuniformity of heterochromatin in the epithelial cells (Fig. 1). The vacuoles contained a somewhat amorphous substance; some of these vacuoles were fused with each other.

The hyperkeratotic palmar papules showed a thickened parakeratotic stratum corneum

*Adaptation to urine as recommended by Dr. Vincent Zannoni.

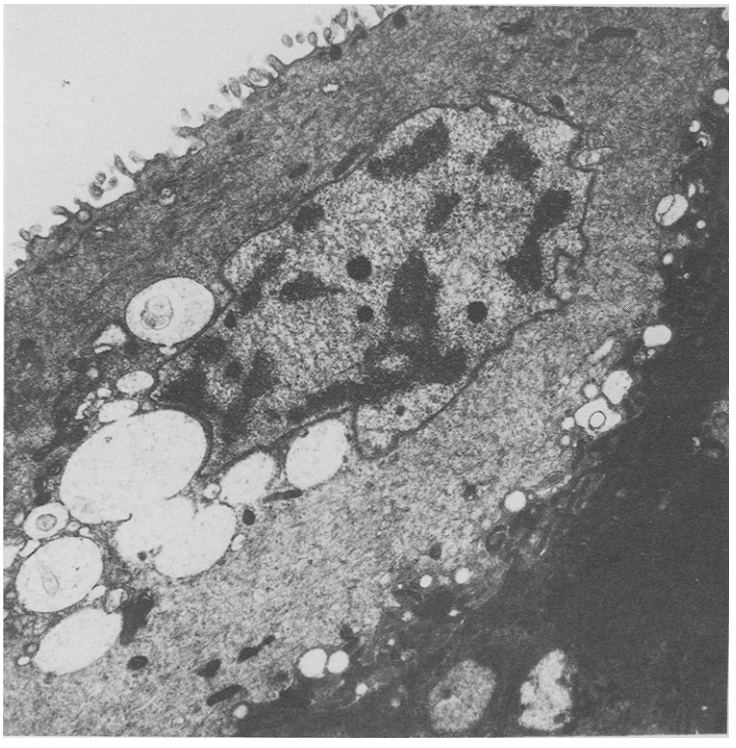

Fig. 1. Epithelial cells of conjunctiva. Note vacuolar structures which are partially membrane delimited and coalescent with each other. The nucleus is indented, and nuclear heterochromatin is not uniformally distributed. (Fixed with osmium-tetroxide and stained with uranyl-acetate and lead citrate. ×6,500.)

with homogeneous refractile eosinophilic inclusions 2 to 3 micra in diameter in the stratum corneum and upper malpighian layer.

Electron microscopic studies of palmar biopsies suggested that the eosinophilic refractile inclusions were lipid-like granules. These granules were of various electron densities and were most prominent in the keratinocytes of the malpighian layer and the stratum corneum. These lipid-like granules measured 2 to 3 micra in diameter and most had a round border, although some had a scalloped border (Fig. 2). Aggregates of complexly whorled and intertwined, discrete filaments were occasionally present close to the plasma membrane of the malpighian cells. Their diameter was about 100 Å, which is different from that of tonofilaments (50 Å). Lipid-like substances and myelin-like figures were seen within these filamentous aggregates (Fig. 3). As in the conjunctivae there was prominent coarse clumping of nuclear chromatin.

RESULTS OF BIOCHEMICAL STUDIES

Fasting plasma tyrosine levels ranged between 1.42 and 1.67 μM per milliliter (normal 0.049 ± 0.003[15]). Tyrosine levels dropped to 0.464 μM per milliliter after two weeks of dietary treatment. Phenylalanine levels were elevated and were between 0.07 and 0.08 μM per milliliter (normal 0.049 ± 0.003[15]). Methionine levels were also normal, measuring 0.03 μM per milliliter (normal 0.019 ± 0.005.[15] Normal values represent mean ± 1 S.D.)

Urinary excretion of tyrosine was as high as 410 mg. per 24 hours. Tubular reabsorption of tyrosine exceeded 99 per cent before and after institution of the low phenylalanine-tyrosine diet. Reabsorption of methionine, isoleucine, and ornithine was lower before than after dietary treatment, but by only 3 to 5 per cent.

Homogentisic acid, homovanillic acid, dihydroxyphenylalanine, dihydroxyphenylacetic

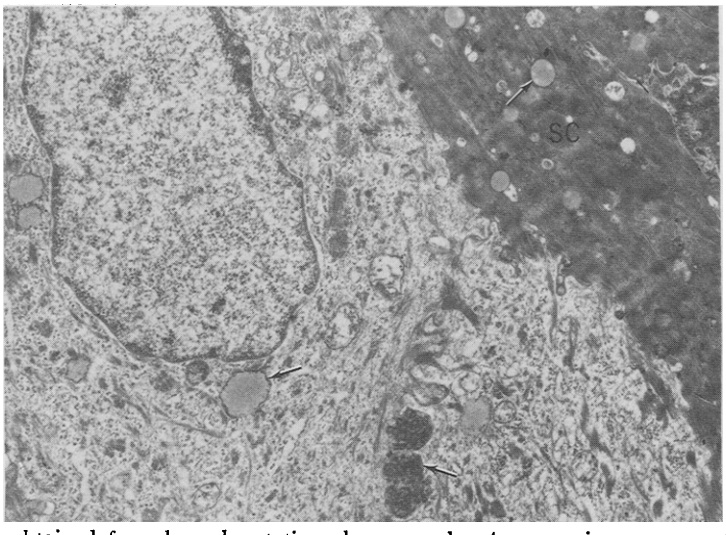

Fig. 2. Skin obtained from hyperkeratotic palmar papule. *Arrows* point to some of the many lipid-like granules (2 to 3 μ in diameter) in the malpighian layer and in the stratum corneum *(SC)*. (Fixed with glutaraldehyde and formaldehyde mixture and stained with uranyl-acetete and lead citrate. ×5,500.)

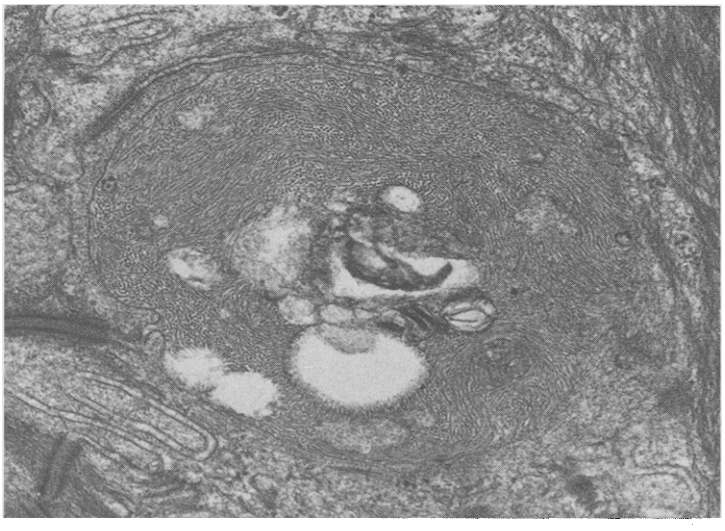

Fig. 3. Skin obtained from hyperkeratotic palmar papule. There is an aggregate of complexly whorled and intertwined, discrete filaments (Ca. 100 Å in diameter) along the plasma membrane of the keratinocytes. Lipid droplet-like substances and myelin-like granules are also prominent in the center of the aggregates. (Fixed with glutaraldehyde and formaldehyde mixture and stained with uranyl-acetate and lead citrate. ×24,500.)

acid, δ-amino levulinic acid, porphobilinogen, OHPAA, phenylpyruvic acid, and glucose and other sugars were not detected in the urine by paper chromatographic methods.

Total tyrosyl substances excreted in the urine as measured by the Millon reaction exceeded 1.4 Gm. per gram of creatinine. Tyrosine and PHPLA accounted for the majority of these substances (Table I).

PHPPA was definitely present in the urine as determined by two methods of study; the enol-borate spectrophotometric study of urine extracts and by comparison of the 2,4-dinitrophenylhydrazone derivatives of urine and standard on silica gel. Two bands (isomers) were obtained from the sample and standard which absorbed maximally at 370 nm. in glacial acetic acid. A 4-fold reduction in

Table I. Summary of clinical and biochemical features of patients with tyrosinemia without hepatorenal disease

Clinical and biochemical features	*Case No. and references*				
	1 (1)	*2 (5, 6)*	*3 (2, 3)*	*4 (4)*	*5 (present report)*
Sex	F	M	F	M	M
Age at report (yr.)	18	2	13	10½	11½
Skin	0	—	Palmar and plantar acrokeratosis onset 8 mo.	—	Palmar and plantar hyperkeratosis
Eyes	Cataracts	Corneal ulcerations, clouding, hyperlacrimation	Corneal ulcerations, onset 6 wk., nystagmus	Severe keratitis up to age 9 mo., severe myopia	Dendritic epithelial corneal clouding, hyperlacrimation, photophobia
Neurologic abnormalities					
Mental status	Retarded	Retarded	Retarded	Retarded	Retarded
Microcephaly	+	+	0	0	+
Others	Self-mutilation, asymmetrical knee reflexes, Babinski on right, seizures				Tics
Other findings	Growth retardation	Cleft palate and lip, inguinal hernias, talipes equinovarus, absence of 1 kidney	History of consanguinity	—	Mild growth retardation, consanguinity
Blood metabolites (mg./100 ml.)					
Tyrosine (normal < 2.5)	7-11	62	25	16-27	25-30
PHPPA (normal 0)	—	0.36	—	—	0
Urinary metabolites (mg./mg. creatinine)					
Tyrosine (normal < 0.05)	0.25	0.32	0.35	0.29	0.56
PHPPA (normal trace)	0.94	0.6-1.8	0.03	0.15	0.46
PHPLA (normal < 0.01)	2.12	1.0-1.7	0.85	0.49	0.90
PHPAA (normal < 0.02)	0.42	0.7-1.2	0.11	0.12	0.11

amount of PHPPA excretion per gram of creatinine was noted two weeks after dietary reduction of phenylalanine and tyrosine.

DISCUSSION

The Richner-Hanhart syndrome is a rare autosomal recessively inherited condition of dendritic corneal opacities, punctate palmar and plantar keratosis, and mental retardation.[16, 17] Metabolic studies have not been reported in these patients.

In this patient with the clinical features of RHS the rapid clearing of the corneal and cutaneous lesions in response to a low-phenylalanine, low-tyrosine diet suggests an etiologic relation between the epithelial lesions and the metabolic defect. Our patients most closely resemble the patient described by Hill and

Zaleski,[2] who had similar metabolic findings, corneal ulcers, and skin lesions which cleared after dietary therapy. Other reported cases with similar clinical and metabolic features are listed in Table I. All of the patients in Table I had mental retardation, eye or skin lesions, and abnormalities in tyrosine metabolism, and we propose that some of the cases reported as atypical tyrosinemia have had the RHS. The variability of the clinical pictures and of some of the metabolic findings, e.g., the low PHPPA in the urine in the patient of Hill and Zaleski, may reflect basic genetic heterogeneity of the basic defects in this group of disorders, the presence of other modifying factors, or methodologic factors which can affect the stability of this compound.

The corneal lesions in our patient were identical to those seen in the six other patients reported with RHS.[16-19] The lesions in RHS are typically dendritic opacities limited to the epithelium. Although the lesions superficially resemble those of herpes simplex, negative viral studies, absence of fluorescein staining, and their stable location over one year of observation rule out that diagnosis. The thickened conjunctival plaques in this patient have not been previously seen in RHS. Definite keratitis was present in three other patients with tyrosinemia (Table I).

The skin lesions in Case 3 (Table I) and in this patient are similar clinically, although the biopsy of Case 3 was interpreted as showing epidermolytic hyperkeratosis. Since our patient does not have epidermolytic hyperkeratosis, as shown by electron microscopic examination, ultrastructural studies of Case 3 could establish if more than one form of epidermal histopathology may be seen in these atypical cases of tyrosinemia.

The conjunctivae and skin had microscopically similar lesions. The abnormal vacuolated cells are similar to those seen in benign familial pemphigus (Hailey-Hailey disease[20]) and after nonspecific injuries like anoxia and ultraviolet light irradiation.[21] The filamentous structures in this patient are unlike those previously described.

Persistent tyrosinemia with the excretion of large amounts of tyrosine and PHPLA and moderate amounts of PHPPA and PHPAA in the absence of cirrhosis or renal tubular dysfunction is compatible with hepatic soluble tyrosine aminotransferase deficiency. In one of the four patients with tyrosinemia without hepatorenal disease[5, 22] soluble tyrosine aminotransferase activity was absent but hepatic mitochondrial tyrosine aminotransferase activity was normal, and hepatic parahydroxyphenylpyruvate hydroxylase activity was intact. We suspect our patient may have this same defect but liver biopsy was not permitted by the patient's family.

Fellman and co-workers[23] suggested a mechanism for the urinary excretion of large amounts of PHPPA in this disease. Distribution of the two enzymes tyrosine aminotransferase and PHPP hydroxylase in tissues indicated an unexpected discordance. PHPP hydroxylase activity was present in human liver and kidney but was absent in muscle, heart, and brain.[23] Mitochondrial tyrosine aminotransferase activity was present in all of these tissues. It was proposed that the elevated plasma tyrosine concentrations resulting from cytosol tyrosine aminotransferase deficiency leads to increased mitochondrial synthesis of PHPPA. Since PHPPA synthesis occurs in many more tissues than does its oxidation, PHPPA accumulates. Thus the source of PHPPA in the urine is extrarenal, and PHPPA is excreted by active tubular secretion.[24, 25]

In rats experimental dietary excess of tyrosine for one week results in the appearance of corneal lesions and hyperkeratotic lesions on the paws very similar to the RHS.[26] During experimental feeding, blood, tissue, and eye concentrations of tyrosine are markedly increased.

Soluble tyrosine aminotransferase is absent prenatally[27]; if the excess of tyrosine and its metabolites are etiologically related to the mental retardation present in RHS, dietary therapy begun early enough in life might prevent mental retardation in these patients.

The autosomal recessively inherited forms of palmar-plantar hyperkeratosis such as RHS are rare, and the painful nature of

the keratotic lesions is a useful clue for suspecting the RHS.

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