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TWO CASES OF TYROSINEMIA TYPE II, AND ITS RARE OCCURRENCE IN TWO BROTHERS

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ABSTRACT

Tyrosinemia type II is a rare autosomal recessive disorder wich can present itself with recurrent epithelial keratitis, hyperkeratotic skin lesions and mental retardation.

This article reports the rare occurrence of this disease in both offsprings (two brothers) of a family (consanguinous marriage) who were managed with a low-protein diet and a special regimen.

Keywords: Richner-Hanhart syndrome, Tyrosinemia type II.

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INTRODUCTION

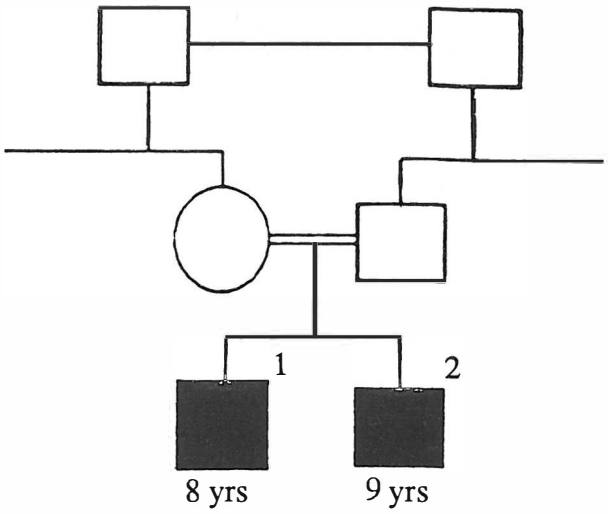
Tyrosinemia type II (Richner-Hanhart syndrome) is a rare metabolic disorder. It is inherited in an autosomal recessive manner, and is caused secondary to a deficiency of hepatic tyrosine aminotransferase. Tyrosinuria and an increase in urinary phenolic acids persist throughout life. Findings include corneal erosions and dendritiform plaques, erosions of the palms and soles and hyperkeratosis. Mental retardation may be present. Treatment includes a low tyrosine, low phenylalanine diet.

CASE REPORT

The patients were two brothers, eight and nine years old, who had suffered from tearing and photophobia since they were about two years old.

Their eye problems were significantly more prominent at night and during the winter or cold weather, and both patients have been under treatment with anti-viral drugs for bilateral herpetic epithelial keratitis for a considerably long time. Upon external examination, their visual acuities were good and their eyes were well aligned. However, due to the extreme photophobia present, a complete eye examination was not possible, hence examination was performed under anesthesia induced by halothane (Fig. 1).

Pedigree of the two cases



In both corneas of the two brothers there were dendritic lesions which stained with fluorescein and rose bengal. No other abnormalities were noticed. The lesions appeared to be epithelial and there was no vascularization (Fig. 2). The remainder of the eye examination, including intraocular

pressure, refraction and fundoscopy was normal.

On general examination, there was hyperkeratosis with hyperhydrosis of the palms and soles (Figs. 3,4). A biopsy was taken from the site and the pathologic report revealed keratoderma with hyperkeratosis, hypergranulosis, and hyperacanthosis without the presence of inflammatory cells, despite the fact that some authors report inflammatory cells in the dermis secondary to irritation (Figs. 5,6).

A variable degree of mental retardation was obvious but the patients had been able to perform their normal regular activities and had successfully completed their first year of schooling. Intelligence quotient (IQ) tests were performed. The elder brother had an IQ of 89-95 (dull normal), and the younger brother had an IQ of 95-105 (normal). Their serum tyrosine levels were 15 mg/dL and 19 mg/dL, respectively, both above normal limits. Normal serum tyrosine levels are shown in Table I.

Due to the above findings, both brothers were referred to the pediatrician as tyrosinemia type II cases.

The above diagnosis was confirmed and treatment was commenced with the exemption of protein in their diet, and by prescribing a fruit and vegetable diet along with the only appropriate milk available in our country (Loflanac)*. Following the commencement of this new diet, within a few weeks the ocular symptoms decreased dramatically, followed later by a decrease in hyperkeratosis, although there was no change in hyperhydrosis (Figs. 7,8). Serum tyrosine levels four months after commencing treatment were 12 and 10.5 mg/dL. During the period of diet control, their problems were minimum but when the regimen was not kept, signs and symptoms would increase dramatically. Sometimes this was noticeable by increased photophobia which was occasionally more severe in one eye and sometimes the symptoms presented themselves as the appearance of pain in the extremities, with or without photophobia.

During our two year follow-up, we noticed that symptoms were more severe during autumn and winter, as well as late afternoons and evenings.

DISCUSSION

Tyrosine is an essential amino acid which enters our body via food (proteins). It is also endogenously synthesized in the body from phenylalanine. It is the precursor of dopamine, norepinephrine, epinephrine, melanin and thyroxine.[1,2] Excess tyrosine in the body is catabolized into water and carbon dioxide. Any discrepancy in this catabolic pathway leads to the disease known as tyrosinemia. Three types of tyrosinemia are known at present:

*Contents: energy 20 kcal/oz; prot 2.2g%; carbohydrate 8.8g%; fat 2.7%; minerals 0.5g% Na+ 14mEq L; K+ 19 mEq/L; Cl-15 mEq/L;Ca 630 mg/L; P 480 mg/L; Fe 13 mg/L.

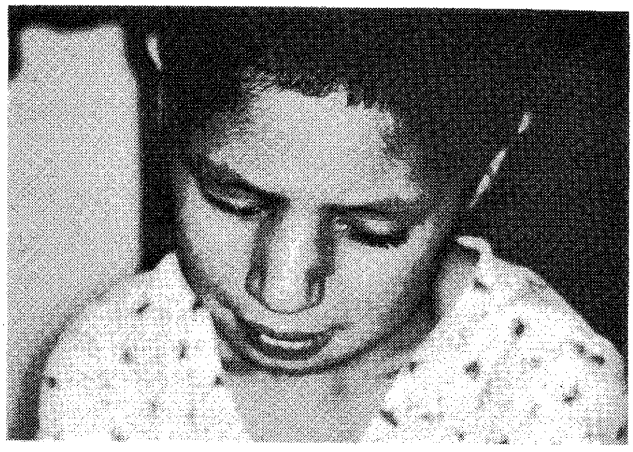


Fig. 1. Photophobia and blepharospasm secondary to epithelial keratitis.

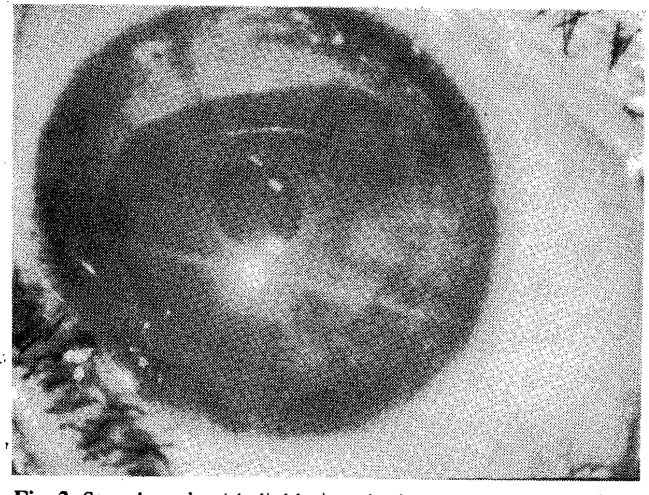


Fig. 2. Star-shaped epithelial lesions in the paracentral area of the cornea which took up faint staining with fluorescein and brilliant staining with rose bengal.

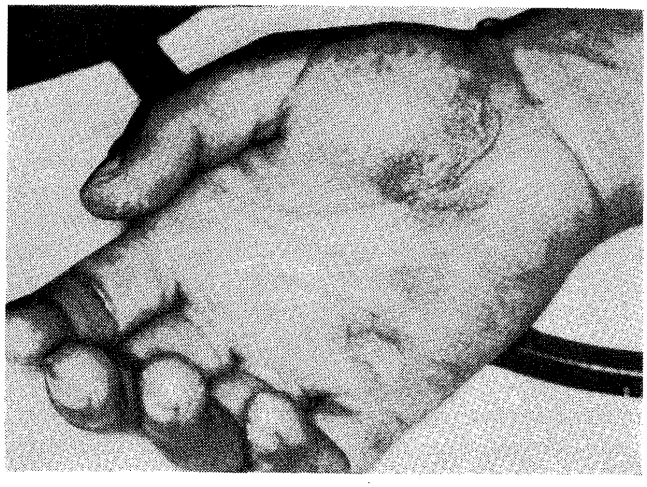


Fig. 3. Hyperkeratotic lesion in hands.

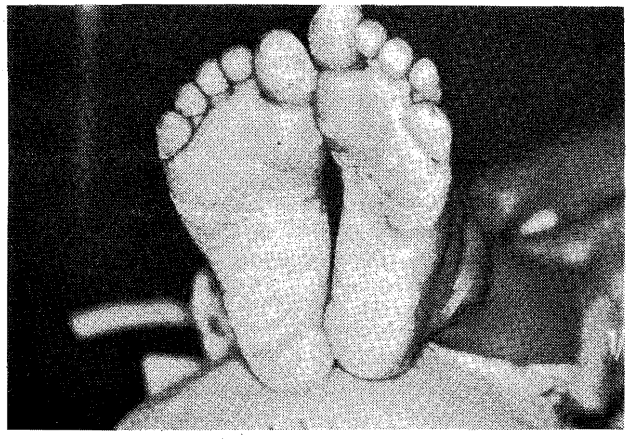
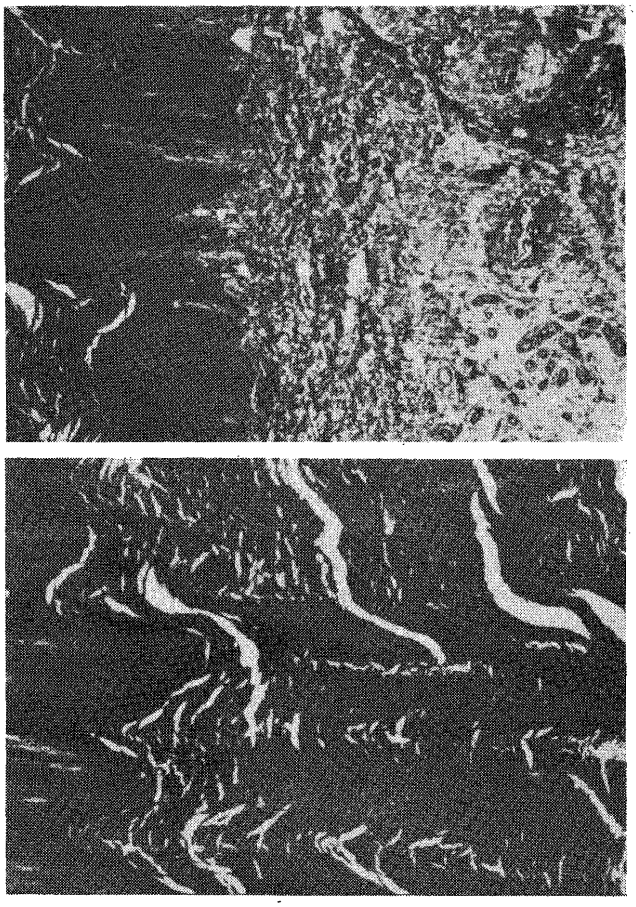


Fig. 4. Hyperkeratotic lesion in feet.



Figs. 5,6. Hyperkeratosis, hypergranulosis and acanthosis are seen. The dermis is normal (H & E stain, magnification × 100).

Table I. Normal tyrosine levels.[1]

Premature neonates	7.0-24 mg/dL	0.390-1.32 mol/L
Mature neonates	1.6-3.7 mg/dL	0.088-0.20 mol/L
Adults	0.8-1.3 mg/dL	0.044-0.07 mol/L

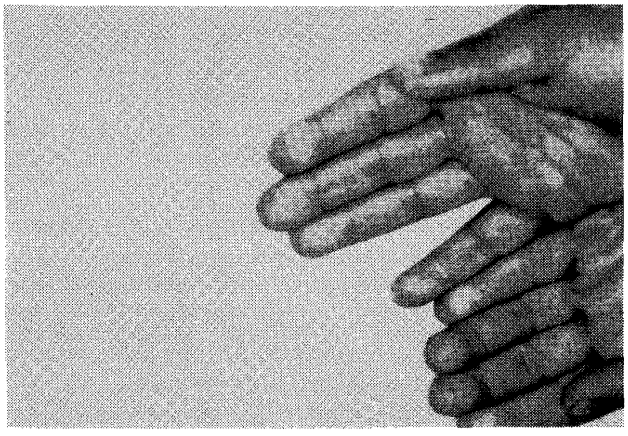


Fig. 7. Improvement in hyperkeratosis of palms four months after initiation of treatment.

Fig. 8. Decrease in photophobia in both brothers four months after initiation of treatment.

A. Type I — also known as hepatorenal, is rare, autosomal recessive in inheritance, and accompanied by an increase in size of the liver and spleen, cirrhosis, vomiting, fever, phosphaturia, glycosuria, aminoaciduria, and renal rickets. It has no ocular or skin lesions.

B. Type II — or Richner-Hanhart syndrome, is also autosomal recessive. It is accompanied by three signs (triad):

1) Recurrent attacks of epithelial or subepithelial pseudodendritic corneal lesions.[3,4]

2) Hyperkeratosis and hyperhydrosis of weight bearing areas of the body (palms, soles and elbows).

3) Variable degrees of mental retardation sometimes accompanied with self mutilation.[1]

C. Type III — a transient form of tyrosinemia which is seen in neonates and has no symptoms.

Type II tyrosinemia or Richner-Hanhart syndrome is seen secondary to deficiency of the enzyme cytosolic tyrosine aminotransferase in the liver.[5] It was first reported by Richner in 1938 and later Hanhart discussed it in a derma-

tology journal in 1947.[6] Till now, not many cases have been reported, and some of them have been from Italian families.[7] Fellman and co-workers pointed out that the main abnormality was a deficiency of the enzyme cytosolic tyrosine aminotransferase (TAT),[6] and this deficiency promoted increased levels of tyrosine in serum and body tissues.

In 1986, Natt and co-workers reported that a TAT deficiency related to human chromosome 16 was genetically responsible.[6] Later Barton and co-workers in the same year pointed out that the locus of TAT is on chromosome 16, locus q 22-24.[6] Although the deficiency exists in the cytoplasm of liver cells, the accumulation of tyrosine and its metabolites is seen throughout the entire body.

Fortunately, with the help of aspartate transaminase, tyrosine can be converted in mitochondria to P-hydroxyphenyl pyruvic acid (P-HPPA), although this is not possible in cells of ectodermal origin.[6] This point explains the reason for the accumulation of tyrosine in keratinized cells of the extremities and cornea. The presence of supersaturated tyrosine in the cell triggers the inflammatory process. Increased tyrosine levels, accompanied by ocular and skin lesions, are seen in tyrosinemia type II.[6]

The triad consisting of ocular symptoms, hyperkeratosis of the palms and soles, and variable degrees of mental retardation, is not always seen together.

Ocular symptoms

These symptoms are seen early in life and may even present in neonates. Heideman and co-workers[8] reported a ten month old child whose ocular problems had commenced when the child was nine months old, a period when the child was weaned from it's mother's milk to the more proteinaceous cow milk. Ocular signs may also present later, and appear as star-shaped intraepithelial or subepithelial corneal opacities which take up faint staining with fluorescein or rose bengal.[8]

Corneal lesions are bilateral, even though one side may be more severe. They differ from herpetic lesions in that the margins are not club-like. The lesions may become vascularized and convert into severe corneal opacities.[8]

Sayar and colleagues[6] reported the histologic findings in one of their patients who underwent penetrating keratoplasty. Toluidine blue staining showed birefringent tyrosine crystals in the corneal stroma. PAS staining showed abnormalities in Bowman's layer and some atypical scarring in the stroma. Inflammatory cells were not seen. In electron microscopy, degeneration of keratocytes was seen. There were some degenerative changes in collagen fibers and they had lost their normal architecture. As tyrosine crystals are water soluble, they were not seen in electron microscopy.

Other ocular findings include whitish conjunctiva, discrete conjunctival plaques, papillary hypertrophy,[9] and subcapsular opacities in the lens.[3] Jaegar and co-workers[10] believe that ocular symptoms become obvious when the serum tyrosine level rises above 10 mg/100mL.

Skin lesions, present as hyperkeratosis accompanied by hyperhydrosis of the palms and soles, are frequently painful and sometimes force the patient to crawl.[11]

The diagnosis is based on clinical findings as well as blood and urine analysis of amino acids. In doubtful cases, a tyrosine loading test can be performed. In such cases, 150 mg/kg of tyrosine is prescribed which increases erythema and pain in the lesions of the extremities, and also increases ocular symptoms.[9]

Treatment consists of a low-protein diet, and ingestion of tyrosine- and phenylalanine-free milk. Twenty-four hours after the commencement of this diet, serum and urinary tyrosine levels both decrease and are accompanied by a decrease in signs of disease. Gradually, in about two to four weeks, photophobia and keratitis improve.[9] Heideman[8] reported that after diet control, there was improvement in keratitis after about a month. Saijo and co-workers[11] have advocated the use of etretinate (Tigason), 80mg daily, and have treated one patient with this regimen. They reported improvement in the patient's hyperkeratosis, but did not record any change in the patient's hyperhydrosis or photophobia.

In conclusion, we believe that all infants presenting with bilateral photophobia and corneal lesions resembling herpes should be evaluated for tyrosinemia type II.

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