Richner–Hanhart syndrome (tyrosinemia type II): a case report of delayed diagnosis with pseudodendritic corneal lesion

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Richner-Hanhart syndrome (tyrosinemia type II) is a rare autosomal recessive disease associated with high serum tyrosine levels caused by the deficiency of tyrosine aminotransferase enzyme. We report a 15-year-old female patient with complaints of bilateral photophobia and tearing, which started during the infancy period. Biomicroscopic examination revealed bilateral circular corneal opacities on the inferior quadrant and small dendritic lesions at the center of the circular opacities. Blood tests showed a tyrosine level of 508 μmol/L (normal range: 30-150). On her dermatologic examination, plantar hyperkeratosis and seborrheic dermatitis were noted, and mild mental retardation was detected. One and a half months after the tyrosine- and phenylalanine-restricted diet, her tyrosine level dropped to 395 μmol/L level, her corneal lesions subsided, and a symptomatic relief was achieved. Tyrosinemia type II should be suspected in patients demonstrating dermatologic signs, especially palmoplantar keratosis, associated with bilateral pseudodendritic corneal lesions unresponsive to antiviral therapy.

Key words: keratitis, palmoplantar keratosis, type II tyrosinemia, tyrosine aminotransferase.

Tyrosinemia type II was first described by Richner in 1938, and the syndrome was then renamed as oculocutaneous syndrome by Hanhart in 1947[1].

Tyrosinemia type II is a rare autosomal recessive disorder of tyrosine metabolism, characterized by elevated plasma levels of tyrosine and its metabolites. The disease incidence has been found to be less than 1/250,000[2]. Bilateral pseudodendritic keratitis, painful palmoplantar hyperkeratosis and mild-to-moderate mental retardation are the main characteristics of this disease. Various symptoms and findings involving the central nervous system are also noted during the course of the disease[2]. The disorder is caused by the deficiency of cytosolic fraction of the liver enzyme tyrosine aminotransferase (TAT). The TAT gene locus is located on chromosome 16q22[3].

Ocular symptoms are epiphora, photophobia and blepharospasm. Corneal haze involving the mid-lower quadrant, pseudodendritic corneal lesions staining poorly with fluorescein, and rarely, corneal or conjunctival plaques are the clinical findings of the disease. Corneal lesions typically do not respond to antiviral therapy. Ocular symptoms heal spontaneously with a relapsing recurring course and are not correlated with other systemic findings[2].

We aimed to present a case referred to our clinic with pseudodendritic keratitis associated with tyrosinemia type II syndrome, who had been previously followed-up with a diagnosis of herpetic keratitis.

Case Report

A 15-year-old female patient admitted to

our clinic in February 2010 with a medical history of epiphora, which had started in the first month of the post-delivery period, and photophobia, which started at the approximate age of five months. Her symptoms seemed to have subsided during the summer, and after the age of two years, because her corneal signs were similar to herpetic keratitis, she was given herpetic infection treatment (topical acyclovir ointment) occasionally when her symptoms became aggravated. Although there were palmoplantar signs, they were not diagnosed by the dermatologist. The patient had ongoing ocular symptoms (epiphora and photophobia) to the present. Her medical history was unremarkable between 2 and 15 years old.

On her ophthalmic examination, visual acuity of the right eye was 4-5/10 with -5.50-1.50x5^0 refractive correction, and visual acuity of the left eye was 5/10 with -6.00-2.00x175^0 refractive correction. Biomicroscopic examination revealed mild bilateral circular corneal hazes located in the mid-lower quadrant of the cornea. Central to these corneal hazes, small dendritic lesions were noted, which stained poorly with fluorescein (Fig. 1). Corneal sensation of both eyes was found to be normal. Biomicroscopic examination of the conjunctiva, anterior chamber, and lens and the funduscopic examination were unremarkable. Therapeutic contact lenses were applied, and artificial tear drops without preservation were prescribed to relieve photophobia and epiphora until a definite diagnosis was established.

Pediatrics consultation revealed an elevated serum tyrosine level of 508 μmol/L (normal limits: 30-150). Analysis of urinary organic acids showed marked elevation of 4-OH-phenyl lactic acid and 4-OH-phenyl pyruvic acid levels. Palmoplantar hyperkeratosis and seborrheic dermatitis were noted on her dermatologic consultation. Overall, a delayed diagnosis of tyrosinemia type II was made at 15 years of age, and mild mental retardation was detected.

A tyrosine- and phenylalanine-restricted diet was initiated by a pediatrician. In two months, her tyrosine level had dropped to 395 μmol/L, her corneal lesions had subsided, and a symptomatic relief was achieved. The patient is still on strict follow-up.

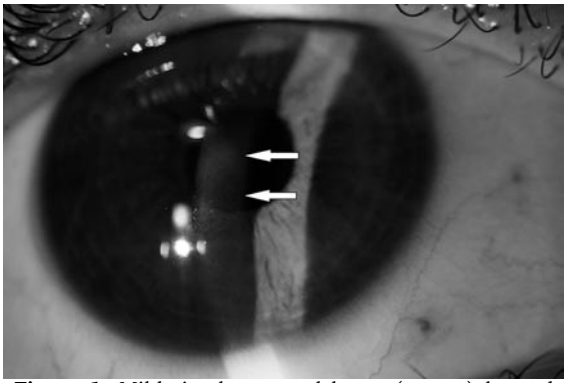

Figure 1. Mild circular corneal hazes (arrows) located in the mid-lower quadrant of the cornea.

Discussion

Hereditary tyrosinemia is classified into three different groups. Type I (fumarylacetoacetate hydrolase deficiency) causes liver and renal diseases, type II (liver tyrosine aminotransferase deficiency) causes oculocutaneous disorders, and type III (4-hydroxyphenylpyruvate dioxygenase) is characterized by normal liver function and episodic central nervous system anomalies. Tyrosinemia type II is the only type with corneal involvement[1].

Previous studies showed that 60% of these patients demonstrated mental deficiency, 75% had corneal involvement, and 80% presented with palmoplantar keratosis[4]. Skin and ocular involvement is caused by the inflammatory response initiated by the intracellular accumulation of tyrosine crystals[5].

Tyrosinemia usually manifests in the first month of life[1]. Macsai et al.[2], in a case series of nine patients, reported that 89% of patients with tyrosinemia type II demonstrated ocular symptoms within the first year of life. In this case series, the youngest patient was 3 months and the oldest patient was 57 years old, and all patients were reported to present with ocular symptoms and findings on the initial visit. Seven (78%) patients were given herpes simplex keratitis treatment before the diagnosis, and 4 (57%) of these 7 patients were reported to show temporary improvement with antiviral treatment. This false improvement was explained by the fact that the pseudodendritic lesions in Richner-Hanhart syndrome typically show a relapsing-recurring course, and this improvement was likely to have arisen by chance during antiviral

therapy. Other conditions that may produce dendritiform epithelial lesions include: herpes simplex virus, varicella-zoster virus, epithelial regeneration line, neurotrophic keratopathy (postherpetic, diabetes mellitus), soft contact lens wear, topical medications (antivirals, beta blockers), acanthamoeba, and epithelial deposits (iron lines, Fabry disease, systemic drugs)[6]. Our case was diagnosed at 15 years of age, and she also received antiviral therapy occasionally when her symptoms became aggravated.

All tyrosinemia type II patients responded to restricted diet therapy, and ocular and skin lesions subsided gradually after treatment[2]. Our case's symptoms also improved with restricted diet therapy.

A general consensus has not been reached about the optimal serum tyrosine levels in these patients[1]. In Macsai's[2] nine-patient case series, only 22% of the patients demonstrated normal levels of serum tyrosine after the treatment.

Seasonal variation in ocular symptoms was included in Richner's description and has been previously described for cutaneous symptoms as well[2].

A meaningful relationship exists between nutritional protein intake and ocular symptoms. In Macsai's[2] study, one patient's vision was markedly better during the summer months, when his main protein source was freshwater bass (6.3 mg tyrosine per gram) than during winter months, when his main protein source was venison (10.7 mg tyrosine per gram)[2]. Our case also reported improvement in her symptoms during the summer. This may be attributed to consumption of less protein and more vegetables and fruit.

In conclusion, tyrosinemia type II should be kept in mind in patients demonstrating bilateral pseudodendritic corneal lesions unresponsive to antiviral therapy, with normal corneal sensation, and associated skin changes like palmoplantar hyperkeratosis.

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