

# Corneal Lesion as the Initial Manifestation of Tyrosinemia Type II

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Tyrosinemia type II (Richner–Hanhart syndrome) is a rare autosomal recessive disease with deficiency of tyrosine aminotransferase and subsequently increasing level of serum tyrosine. We report the case of a 2-year-old girl who was referred due to bilateral corneal lesions. Slit-lamp examination showed small granular white deposits arranged in a dendritic pattern in the superficial central cornea of both eyes. Physical examination revealed painful, non-pruritic, hyperkeratotic plaques on the soles, palms and fingertips. Mental evaluation demonstrated developmental delay for her age. Blood examination revealed serum tyrosine level to be 1,868  $\mu\text{M}$  (normal range, 30–110  $\mu\text{M}$ ), which decreased to 838  $\mu\text{M}$  with 2-month diet on tyrosine and phenylalanine restriction. The corneal and skin lesions resolved completely. However, the corneal deposits recurred a month later as her mother failed to strictly control the diet because the little girl was losing weight and activity. With specific formula and adjusted diet regimen, the corneal lesions decreased again. Corneal pseudodendritic deposits may be the initial manifestation in patients with tyrosinemia type II. Early diagnosis and intervention with diet control are crucial for preventing permanent visual and developmental deficits. Corneal deposits can be one of the parameters in monitoring the efficacy of diet control. [J Chin Med Assoc 2006;69(6):286–288]

**Key Words:** cornea, pseudodendritic, Richner–Hanhart syndrome, tyrosinemia type II

## Introduction

Tyrosinemia type II was first described by Richner<sup>1</sup> in 1938 and later by Hanhart<sup>2</sup> in 1947 as an oculocutaneous syndrome. It is characterized by bilateral pseudodendritic keratitis, painful palmoplantar hyperkeratotic lesions, mental retardation, and variable manifestations of central nervous system involvement. It is an inborn error of metabolism with deficiency of hepatic cytosolic tyrosine aminotransferase (TAT), the rate-limiting enzyme of tyrosine catabolism. Patients have elevated tyrosine blood levels and an increase in urinary tyrosine metabolites. The TAT gene locus was assigned to chromosome 16q22.<sup>3</sup>

Tyrosinemia type II can be detected by screening in the newborn; however, the test is not routinely performed because the disease is extremely rare. Delay in

diagnosis may result in permanent visual impairment and mental retardation. Therefore, awareness of the initial presentation of the disease in order to make an early diagnosis is very important. We report a patient who presented with ocular symptoms and signs as the initial manifestation. Follow-up of the ocular signs can help in monitoring the control of tyrosinemia.

## Case Report

A 2-year-old girl was referred due to bilateral dendritic corneal lesions. She was described by her mother as being reluctant to open her eyes in the afternoon. The patient was found to have photophobia and frequent tearing since birth. Herpetic keratitis was diagnosed but treatment was not effective.

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Slit-lamp examination revealed small granular white deposits arranged in a dendritic pattern in the superficial central cornea of both eyes (Figure 1A). The lesions did not stain with fluorescein (Figure 1B). The conjunctiva was not congested. The anterior chamber, pupil, lens and fundus in both eyes were normal.

Physical examination showed painful, non-pruritic, hyperkeratotic plaques on the soles, palms and fingertips (Figure 2A). Blood examination revealed serum tyrosine level to be 1,868  $\mu\text{M}$  (normal range, 30–110  $\mu\text{M}$ ). Urinary organic acid analysis showed marked elevation of tyrosine metabolites, and the urine tyrosine level was 1,765  $\mu\text{M}$ . No other significant laboratory abnormalities were detected. Thus, the diagnosis of tyrosinemia type II was made.

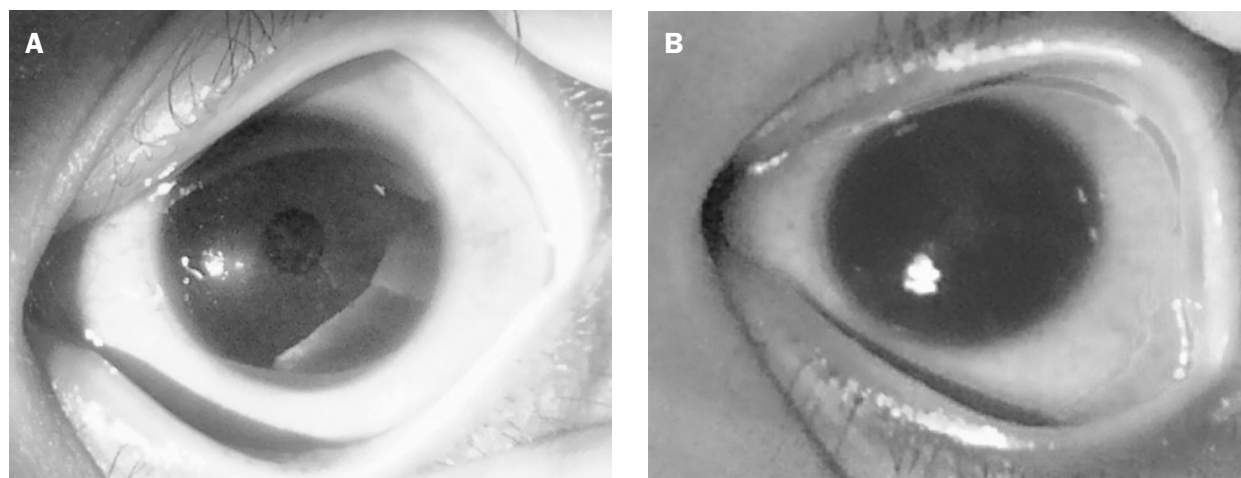
Brain magnetic resonance imaging (MRI) showed suspected demyelination of white matter. According to the *Bayley Scales of Infant Development* (2<sup>nd</sup> edition), her mental developmental index score was 56 (normal range, 85–114), which demonstrated significant delay for her age. Both her parents and older sister were free

from any ocular or cutaneous lesions. There was no consanguinity of the parents.

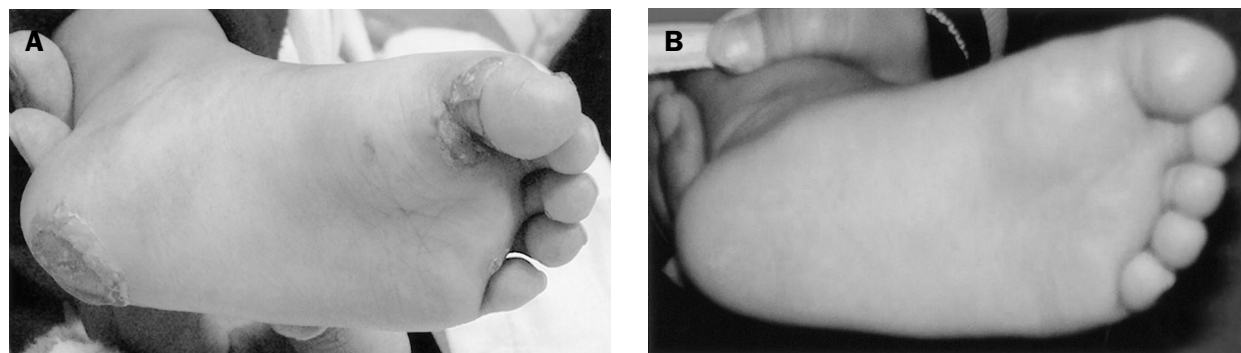
She immediately underwent a tyrosine and phenylalanine restriction diet. Two months later, her serum tyrosine level had decreased to 838  $\mu\text{M}$ , and the corneal and skin lesions had resolved completely (Figure 2B). Her mental status and language capability had also improved. However, the corneal lesions recurred 1 month later as her mother had failed to keep strict diet control for fear of weight loss in the already thin girl. By using a specific formula and adjusting the diet regimen, the corneal deposits progressively cleared.

## Discussion

Inherited tyrosinemia is classified into type I (deficiency of fumarylacetoacetate hydrolase) with hepato-renal diseases, type II (deficiency of hepatic tyrosine aminotransferase) with oculocutaneous diseases, and



**Figure 1.** (A) External photograph of the left eye showing dendritiform lesions in the central cornea. (B) The lesions stained negatively with fluorescein.



**Figure 2.** (A) Painful, non-pruritic, hyperkeratotic plaques on the sole. (B) Two months after diet control, the skin lesions resolved completely.

type III (deficiency of 4-hydroxyphenylpyruvate) with normal liver function and intermittent neurologic anomalies. All types demonstrate elevated blood tyrosine levels, but only type II is associated with corneal changes.

Tyrosinemia type II usually manifests in the first month of life. A previous study reported that palmoplantar keratosis occurred in 80%, corneal lesions in 75%, and mental retardation in 60% of reported cases.<sup>4</sup> Ocular symptoms include photophobia, tearing, redness and blepharospasm. A recent series described 9 patients: all presented with ocular manifestations but only 56% had skin lesions at the time of diagnosis.<sup>5</sup> The corneal and skin lesions are thought to be an inflammatory response secondary to the deposition of tyrosine crystals.<sup>6</sup> The dendritiform corneal lesions are frequently misdiagnosed as herpetic keratitis. Seven of the 9 patients (78%) reported by Macsai et al<sup>5</sup> together with the patient in this report were initially diagnosed and treated for herpes simplex keratitis. The corneal lesions may undergo spontaneous remission and recurrence, giving the illusion of a clinical response to antiviral treatment. These pseudodendrites may occur without skin lesions, making the misdiagnosis of herpes simplex virus keratitis more likely. The lack of terminal bulbs, poor staining with fluorescein, bilateral involvement, poor response to antiviral agents, persistent inferocentral location of the dendrites, normal corneal sensation, and exacerbation of symptoms with increased dietary protein may help in the differential diagnosis from viral dendritic lesions.

A low tyrosine and low phenylalanine diet is currently the most effective treatment for tyrosinemia type II to reverse the ocular and skin manifestations. However, a strict low tyrosine and low phenylalanine diet without a specific formula may sometimes lead to protein intake deficiency, as occurred in our patient, which makes dietary compliance difficult. There is no consensus as to what is the optimal blood tyrosine level, or at what age the diet should be started to prevent neurologic impairment. The blood tyrosine level is suggested to be < 500  $\mu\text{M}$ . Of the 9 cases reported by Macsai et al,<sup>5</sup> all 3 cases with controlled blood tyrosine < 500  $\mu\text{M}$  were normal in both ocular and developmental conditions, 3 cases with peak tyrosine level between 500 and 900  $\mu\text{M}$  were also asymptomatic, but 1 patient with peak tyrosine level > 1,000  $\mu\text{M}$  showed recurrence of corneal lesion and low intelligence. Other reports have suggested the initiation of dietary treatment in infancy to maintain serum tyrosine concentrations between 300 and

800  $\mu\text{M}$  with occasional peaks < 1,000  $\mu\text{M}$ , which is associated with normal psychomotor development.<sup>7,8</sup>

Early dietary control is as important as serum tyrosine levels in determining outcome. Strict dietary control achieved as early as 40 months of age may be inadequate to prevent some language disorders.<sup>9</sup> Delay in dietary therapy as well as poor dietary compliance may result in chronic keratitis and corneal scarring. The corneal lesions can recur in a corneal transplant, particularly if systemic steroids are used.<sup>10</sup>

In conclusion, bilateral pseudodendritic keratitis may be the initial manifestation of tyrosinemia type II. Early screening of infants with this manifestation and strict dietary intervention are vital for successful treatment. Regular follow-up of the corneal lesions to check blood tyrosine levels and adjust the dietary regimen can help enhance dietary compliance and prevent morbidity associated with inadequate protein intake.

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