



## A child with dendritiform eye lesions and developmental delay

Vasiliki Gliagias, MD<sup>a</sup>, Ksenia Denisova, MD<sup>b</sup>, Joann J. Kang, MD<sup>b,\*</sup>

<sup>a</sup> Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Hempstead, NY, USA

<sup>b</sup> Department of Ophthalmology and Visual Sciences, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY, USA

### ARTICLE INFO

#### Keywords:

Tyrosinemia  
Tyrosinemia type II  
Dendritiform lesions  
Epithelial defects  
Oculocutaneous tyrosinemia

### ABSTRACT

**Purpose:** Tyrosinemia Type II (Richner-Hanhart syndrome) is a rare autosomal recessive disease that occurs due to deficiency in the enzyme tyrosine aminotransferase and can result in an ulcerated keratitis. We present a case of a young patient with oculocutaneous tyrosinemia despite a negative newborn screen.

**Observations:** A 15 month old boy with an uncomplicated birth history and negative newborn screen presented with a unilateral central irregular epithelial defect and hyperkeratotic lesions on his fingertips and soles. A month later, the patient developed bilateral dendritiform epithelial erosions. Following a series of antiviral, antibiotic, and lubricating treatments, there was a waxing and waning course of epithelial healing. After the patient was lost to follow up for one year, the patient presented with a new global developmental delay prompting further workup. Tyrosine and phenylalanine levels were ordered which confirmed a diagnosis of Tyrosinemia Type II, and the patient was started on a low-protein diet. A month later, the patient's epithelial defects and ocular symptoms were resolved.

**Conclusion and Importance:** Presentation of a dendritiform epithelial erosion, whether unilateral or bilateral, accompanied by symptoms of developmental delay and palmoplantar hyperkeratotic lesions should prompt measurement of tyrosine and phenylalanine levels. As dermatologic lesions and variable developmental delay may not appear until later in the course of disease, diagnosis may depend on early recognition of ocular signs and symptoms even with negative newborn screening. Prompt diagnosis and diet modification is necessary to prevent developmental delay in this disease. To our knowledge, this is the first Tyrosinemia Type II case in the literature manifesting as an asynchronous bilateral eye disease.

### 1. Background

Tyrosinemia Type II (Richner-Hanhart syndrome) is a rare autosomal recessive disease that occurs due to deficiency in the enzyme tyrosine aminotransferase, which decomposes phenylalanine and tyrosine.<sup>1</sup> As a result of the enzyme deficiency, tyrosine and its metabolites accumulate in the keratin cells of the hands, feet and corneal epithelium, where the intracellular crystallization of tyrosine is thought to initiate inflammation.<sup>2</sup> Unlike Tyrosinemia Type I which does not have corneal findings, corneal changes in Type II are seen as bilateral superficial punctate crystalline deposits that may assume a dendritiform pattern. This may lead to an ulcerated keratitis, which may be mistaken for herpes simplex keratitis.<sup>3</sup> Over time, peripheral vascularization, irregular epithelium and corneal haze may develop. These findings typically present months before hyperkeratotic skin lesions on hands and feet (palmoplantar keratosis) appear.<sup>4</sup> Accompanying signs and symptoms include photophobia, nystagmus, strabismus, conjunctival thickening, and cataract.<sup>4</sup>

Patients may have variable mental disability but have normal hepato-renal function (in contrast to Type I disease).

We present a case of a young patient with oculocutaneous tyrosinemia despite a negative newborn screen. To our knowledge, this is the first Tyrosinemia Type II case in the literature manifesting as an asynchronous bilateral eye disease. Previous reports have only documented lesions presenting bilaterally, in contrast to our patient's initial presentation with a unilateral disease which later developed in the contralateral eye.

### 2. Case presentation

A 15 month old boy was referred by his pediatrician for possible corneal abrasion or ulcer in the left eye. The mother reported that he had one month of light sensitivity, tearing and eye rubbing which had not improved on erythromycin ointment. The child also recently developed hyperkeratotic plaques on his fingertips and soles (Fig. 1A and B). The

\* Corresponding author.

E-mail address: [jokang@montefiore.org](mailto:jokang@montefiore.org) (J.J. Kang).

<https://doi.org/10.1016/j.ajoc.2022.101701>

Received 17 June 2022; Received in revised form 29 August 2022; Accepted 1 September 2022

Available online 6 September 2022

2451-9936/© 2022 Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

child was born full-term via normal spontaneous vaginal delivery with an uncomplicated course and negative newborn screen. At 3 months old, he was found to have an accessory urethra which was removed by surgical excision without complication.

Initial left eye examination revealed a 2 mm central irregularly shaped epithelial defect with punctate staining and underlying haze. The patient was started on moxifloxacin four times a day. On one week follow up, there was heaped up epithelial irregularity without staining and erythromycin ointment was restarted. About a month later, bilateral central dendritic-like epithelial defects were found. He then had a waxing and waning course of epithelial healing with treatment including oral acyclovir, ganciclovir gel, moxifloxacin eye drops and lubricating drops and ointment. The patient was subsequently lost to follow up and returned over a year later with an epithelial defect in a dendritiform pattern in the left eye. Herpes Simplex Virus 1/2 IgM and IgG titers were found to be negative. Additionally, the child was now noted to have a new global developmental delay and poor appetite and oral intake. Due to high suspicion, further workup with serum tyrosine and phenylalanine levels was obtained.

The patient had an elevated tyrosine level of 1958 (normal: 24–115). He was referred to genetics and was molecularly confirmed for Tyrosinemia Type II. Additionally, it was found he had a pedigree with positive consanguinity (parents are first cousins). He was started on a low tyrosine and phenylalanine diet. Following a month of diet modification, tyrosine levels were controlled. The patient's epithelial defects markedly resolved, and the mother reported cessation of ocular symptoms.

### 3. Discussion and conclusions

This patient's diagnosis of tyrosinemia was delayed due to a preliminary diagnosis of herpes simplex epithelial keratitis and negative newborn screen. Primary ocular herpes simplex infection occurs in the form of vesicular blepharconjunctivitis both in neonates through birth canal transmission and in children through orofacial mucus membrane transmission. Primary infection is often self-limiting, and the virus ascends through the cutaneous nerves and stays latent in the trigeminal nerve ganglion.<sup>5</sup> Upon reactivation, a secondary infection happens involving eyelids, conjunctiva, cornea, uvea, and rarely retina.<sup>6</sup> Most commonly, reactivation manifests as epithelial dendritic keratitis.<sup>6</sup>

The hallmark of herpes simplex epithelial keratitis is a true dendritic ulcer with a branching linear shape with terminal bulbs and swollen epithelial borders that contain live virus. The base of the ulcer stains positively with fluorescein. Although the epithelial borders stain

negatively with fluorescein, they can be demarcated with rose bengal.<sup>6</sup> This patient presented with a unilateral irregularly shaped epithelial defect with punctal staining and underlying haze that later evolved to bilateral central dendritic-like epithelial defects.

The patient's initial presentation was not characteristic of a true dendritic ulcer (without a linear branching pattern and terminal bulbs), therefore antibiotic treatment was initiated. Despite antibiotic treatment, the progression to bilateral dendritiform epithelial defects led to a preliminary diagnosis of herpes simplex keratitis. While rare in adults, bilateral disease occurs at a higher rate in children.<sup>7,8</sup> The patient's waxing and waning course of epithelial healing did not initially raise concern for misdiagnosis as children are more susceptible to recurrences of ocular herpes, with studies showing that half of all children with herpes simplex keratitis develop a keratitis recurrence within 1–2 years.<sup>7</sup>

Other causes of dendritiform epithelial lesions in the herpes family were also considered in the diagnosis of this patient. Herpes zoster is rare in early childhood, and most of the reported cases are related to immunosuppression or intrauterine acquired infection leading to varicella in the immediate neonatal period or herpes zoster during infancy.<sup>8</sup> Varicella zoster virus can present with punctate keratitis and pseudodendrites which lack terminal bulbs and dichotomous branching, in contrast to herpes simplex dendrites.<sup>9</sup> These pseudodendrites stain poorly with both fluorescein and rose bengal. However, in herpes zoster ophthalmicus, a vesicular rash in the dermatomal distribution of the trigeminal nerve would be expected, which was not seen in our patient.<sup>10</sup>

A year after initial presentation, when the patient returned after missing follow up, the patient was noted to have new global developmental delay. This new finding in the setting of poor response to antiviral therapy, prompted further workup with serum tyrosine and phenylalanine levels, leading to a diagnosis of Tyrosinemia Type II. Several factors contributed to a delayed diagnosis, including a negative newborn screen ruling out tyrosinemia, lack of developmental delay at initial presentation, and a dendritiform corneal epitheliopathy resembling herpes simplex epithelial keratitis that waxed and waned with treatment. The patient did have hyperkeratotic lesions on his fingers and toes that developed 1 month after onset of ocular symptoms, however the significance of this only became clear once the child developed global developmental delay.

Cases of Tyrosinemia Type II have been published in the literature before, with age of diagnosis ranging from 5 months to 57 years of age.<sup>11</sup> In the outlier 57-year old case, symptom severity corresponded to level



Fig. 1. A. Hyperkeratotic plaques on the patient's fingertips and palms. B. Hyperkeratotic plaques on the patient's toe and sole.

of dietary protein consumption, which was seasonal for the patient. Palmoplantar keratosis was reported to occur in 80% of cases, followed by corneal lesions in 75%, and mental retardation in 60% of cases.<sup>12</sup> Corneal lesions have been reported at as young as 1 month of age.<sup>11</sup> Ocular and cutaneous defects resolved completely if patients followed a strict modification of diet.<sup>1-4,11-16</sup> Recurrence has been documented following a lapse in dietary modification.<sup>11</sup>

Similar to the present report, in most cases patients were suspected to have a diagnosis of herpes simplex keratitis, and treatment with acyclovir was given.<sup>2-4,11-14</sup> Some patients were found to have transient resolution of corneal findings following antiviral therapy, however only completely resolved with dietary therapy.<sup>11</sup> In all reported cases, corneal lesions were found bilaterally at initial presentation. It is unknown why our patient initially presented with unilateral findings, as metabolite accumulation in the corneal epithelium would be hypothesized to occur equally in both eyes. It can be speculated that this metabolic deposition was subclinical in the contralateral eye at the time of evaluation. Furthermore, Tyrosinemia Type II has also been documented with cutaneous manifestations and no ophthalmic findings.<sup>17,18</sup> Cutaneous symptoms typically appear after the first year of life, so they cannot be relied upon for diagnosis.<sup>19</sup>

As in our patient, Tyrosinemia may not be detected by newborn screening when

specimens are collected in the first few days of life as tyrosine levels may not be sufficiently elevated for detection by tandem mass spectrometry.<sup>20</sup>

Tyrosinemia Type II is a rare autosomal recessive disease and its ocular manifestation is commonly misdiagnosed as herpes simplex keratitis. A unilateral or bilateral presentation of dendritiform epithelial erosions accompanied by developmental delay and palmoplantar hyperkeratotic lesions should prompt measurement of tyrosine and phenylalanine levels. However, as dermatologic lesions and variable developmental delay may not appear until later in the course of disease, diagnosis may depend on early recognition of ocular signs and symptoms even with negative newborn screening. Prompt diagnosis and diet modification is necessary to prevent developmental delay.

#### Patient consent

Consent to publish this case report has been obtained from the patient's guardian in writing.

#### Funding

No funding or grant support.

#### Authorship

All authors attest that they meet the current ICMJE criteria for

Authorship.

#### Declaration of competing interest

JJK: Sanofi (C).

The following authors have no financial disclosures: VG, KD.

#### Acknowledgements

None.

#### References

- Al-hemidan AI, Al-hazzaa SF. Richner-Hanhart syndrome (tyrosinemia type II) case report and literature review. *Ophthalmic Genet.* 1995;16(1):21–26.
- Al-Rashed WA, Kalantan HA, Al-Ahmadi AS. Bilateral pseudodendritic keratitis: a presentation of tyrosinemia type II. *Middle East Afr J Ophthalmol.* 2007;14(2):73–75.
- Tsai CP, Lin PY, Lee NC, et al. Corneal lesion as the initial manifestation of tyrosinemia type II. *J Chin Med Assoc.* 2006;69(6):286–288.
- Gokhale NS, Dherai AJ, Desai H, et al. Unusual dendritic keratitis. *Indian J Ophthalmol.* 2007;55(1):57–59.
- Wilhelmus KR, Falcon MG, Jones BR. Bilateral herpetic keratitis. *Br J Ophthalmol.* 1981;65(6):385–387.
- Kanukollu VM, Patel BC. Herpes simplex ophthalmicus. Available at <https://www.ncbi.nlm.nih.gov/books/NBK559194>. Accessed September 10, 2021.
- Chong EM, Wilhelmus KR, Matoba AY, et al. Herpes simplex virus keratitis in children. *Am J Ophthalmol.* 2004;138(3):474–475.
- Gupta LK, Khare AK, Mittal A, et al. Herpes zoster in infancy. *Indian Dermatol Online J.* 2013;4(3):252–254.
- Liesegang TJ. Herpes zoster ophthalmicus natural history, risk factors, clinical presentation, and morbidity. *Ophthalmology.* 2008;115(2):S3–S12.
- Sampathkumar P, Drage LA, Martin DP. Herpes zoster (shingles) and postherpetic neuralgia. *Mayo Clin Proc.* 2009;84(3):274–280.
- Macasai MS, Schwartz TL, Hummel MB, Mulhern MG, Rootman D. Tyrosinemia type II: nine cases of ocular signs and symptoms. *Am J Ophthalmol.* 2001;132(4):522–527.
- Buist NR, Kennaway NG, Fellman JH. Tyrosinaemia type II. In: Bickel H, Wachtel V, eds. *Inherited Diseases of Aminoacid Metabolism.* Stuttgart: Thieme; 1995:203–235.
- Charlton KH, Binder PS, Wozinak L, Digby DJ. Pseudodendritic keratitis and systemic tyrosinemia. *Ophthalmology.* 1981;88(4):355–360.
- Martin GC, de Lonlay P, Chapron T, Cochereau I, Caputo G, Gabison E. Bilateral dendriform ulcer leading to an early diagnosis of tyrosinemia type 2. *J AAPOS.* 2020;24(2):120–122.
- Valikhani M, Akhyani M, Jafari AK, Barzegari M, Toosi S. Oculocutaneous tyrosinaemia or tyrosinaemia type 2: a case report. *J Eur Acad Dermatol Venereol.* 2006;20(5):591–594.
- Paige DG, Clayton P, Bowron A, Harper JL. Richner-Hanhart syndrome (oculocutaneous tyrosinemia, type II). *J R Soc Med.* 1992;85(12):759–760.
- Shimizu N, Ito M, Ito K, et al. Richner-Hanhart's syndrome: electron microscopic study of the skin lesion. *Arch Dermatol.* 1990;126(10):1342–1346.
- Lestringant GG. Tyrosinemia type II with incomplete Richner-Hanhart's syndrome. *Int J Dermatol.* 1988;27(10):43–44.
- Meissner T, Betz RC, Pasternack SM, et al. Richner-Hanhart syndrome detected by expanded newborn screening. *Pediatr Dermatol.* 2008;25(3):378–380.
- la Marca G, Malvagia S, Pasquini E, et al. Newborn screening for tyrosinemia type I: further evidence that succinylacetone determination on blood spot is essential. *J Inherit Metab Dis.* 2011;1:107–109.