Presumed Atypical HDR Syndrome Associated With Band Keratopathy and Pigmentary Retinopathy

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ABSTRACT
This report describes presumed atypical hypoparathyroidism, deafness, and renal dysplasia (HDR) syndrome associated with unexpected ocular findings. The patient had exotropia, bilateral band keratopathy, and pigmentary retinopathy, including attenuated retinal vessels and atrophy of the retinal pigment epithelium. Even though the calcific plaques were successfully removed, visual acuity in both eyes gradually decreased and electroretinography was extinguished.

INTRODUCTION
The clinical combination of hypoparathyroidism, deafness, and renal dysplasia was first described in 1977. However, it was not until several years later that it was recognized as a specific clinical entity and named “HDR syndrome.” HDR syndrome is an autosomal dominant disorder caused by mutations of the GATA3 gene, which is located on chromosome 10p15. GATA3 belongs to the dual zinc finger transcription factor family, which is involved in vertebrate embryonic development.

This report describes the first case of presumed atypical HDR syndrome associated with exotropia, bilateral band keratopathy, and abnormal fundus appearance, including attenuated retinal vessels and granularity and atrophy of the retinal pigment epithelium.

CASE REPORT
A 9-year-old girl presented with corneal opacity in both eyes. At 4 years of age, she had a generalized tonic seizure and laboratory examination showed hypocalcemia, hypoparathyroidism, and proteinuria. Proteinuria persisted despite intensive treatment with steroid and immunosuppressive drugs. The family history was unremarkable. Renal ultrasonography showed bilateral tiny multiple cysts in the renal medullae, and voiding cystourethrogram showed bilateral grade IV vesicoureteral reflux. She was treated with oral calcitriol and calcium supplementation. Renal function decreased rapidly, and peritoneal dialysis for end-stage renal disease was started at 6 years of age.

On the first examination for bilateral conjunctival injection at 9 years of age, best-corrected visual acuity in the right and left eyes was 20/32 and 20/50, respectively. She had exotropia of 25 prism diopters at distance and 20 prism diopters at near with correction. Examination of the cornea showed band calcific plaques in both eyes (Figs. 1A and 1B), and fundus examination showed retinal pigment epithelium with a granular appearance. Ten months later, best-corrected visual acuity decreased to 20/63 and 20/100 in the right and left eyes, respectively. Surgery for bilateral band keratopathy was performed with amniotic membrane transplantation. Two months after surgery, uncorrected visual acuity improved to 20/32 and 20/40 in the right and left eyes, respectively.

At 12 years of age, abdominal imaging showed multiple renal cysts in both kidneys, and pure tone audiometry showed bilateral sensorineural hearing loss. GATA3 gene analysis showed no pathogenic mutation, but showed a known polymorphism, heterozygous IVS5+60C>T.

The patient is scheduled for kidney transplantation. The latest eye examination was performed 2
years after surgery for band keratopathy. Although the cornea was clear (Figs. 1C and 1D), best-corrected visual acuity decreased to 20/63 in both eyes and fundus examination showed attenuated retinal vessels and increased granularity and atrophy of the retinal pigment epithelium in both eyes (Fig. 2). Photopic and scotopic electroretinography showed no response in either eye (Fig. 3).

**DISCUSSION**

The current patient presented with bilateral band keratopathy, which in children is usually observed in patients with hypercalcemia caused by hyperparathyroidism or juvenile rheumatoid arthritis–associated uveitis. However, she also had hypocalcemia and hypoparathyroidism, which are associated with HDR syndrome. Bilateral band keratopathy in patients with hypocalcemia is rare, but has been reported in Kenny–Caffey syndrome. This syndrome is characterized by hypoparathyroidism, short stature, osteosclerosis, and eye abnormalities, including bilateral band keratopathy, and associated with mutations of...
the tubulin-binding chaperone E (TBCP) gene located on chromosome 1q42.3. HDR syndrome and Kenny–Caffey syndrome overlap because both involve inherited hypoparathyroidism and are associated with bilateral band keratopathy that may occur at an early age, despite hypocalcemia.

The reason band keratopathy can occur in patients who have hypocalcemia in association with hypoparathyroidism is not known. It appears that large fluctuations in serum calcium levels or calcium dysregulation caused by the mutation of a gene involved in embryonic development may play a more significant role than the absolute serum calcium level in the pathogenesis of bilateral band keratopathy in these syndromes. Another possibility is that calcific plaques in these syndromes may not be composed of pure calcific components, but rather of mixed byproducts of the calcium metabolic pathway. Previous histologic analysis of band keratopathy showed that it is either calcific, noncalcific, or a mixture of both. Analysis further identified noncalcific bands as being composed of the products of elastic collagen degeneration.

An abnormal fundus is an intriguing unexpected finding in the current patient. Findings include attenuated retinal vessels and granularity and atrophy of the retinal pigment epithelium. These findings resemble the fundus findings of retinitis pigmentosa. In the current patient, visual acuity improved after successful band keratopathy surgery. However, during follow-up after surgery, visual acuity gradually decreased, although there was no evidence of recurrence of band keratopathy. Moreover, electroretinography after 34 months of follow-up showed no response in either eye. Therefore, the patient’s reduced best-corrected visual acuity was attributed to progressive retinal involvement.

Mutations of the GATA3 gene in HDR syndrome include total gene deletions, missense mutations, nonsense mutations, abnormal splicing mutations, and small intragenic deletions. Direct sequencing of all coding exons of the GATA3 gene was performed. This sequencing cannot detect heterozygous total gene deletion. However, the presence of heterozygous intronic polymorphism in the patient can exclude the possibility of total gene deletion.

The previous report of GATA3 analysis in nine Japanese families with HDR syndrome by Muroya et al. showed that no GATA3 abnormalities were identified in two families and that HDR syndrome has a wide phenotypic spectrum. In these two families with no GATA3 abnormalities, one patient had bilateral retinitis pigmentosa and severe short stature (−4.4 standard deviations), which were absent in other family members. Therefore, it seems that the current patient is similar to the case reported by Muroya et al. because both had bilateral retinal involvement without known GATA3 gene mutation. However, the current patient had other ophthalmic findings, such as strabismus, band keratopathy, and extinguished electroretinography findings, which were not reported by Muroya et al., who mentioned retinitis pigmentosa but did not provide details about the ophthalmic findings or the results at follow-up.

Although the current patient fulfills the phenotypic criteria for HDR syndrome, GATA3 gene analysis showed no pathogenic mutation. In addition, this patient has unusual ocular involvement, which has not typically been shown in HDR syndrome. Therefore, the current patient may be presumed to have atypical HDR syndrome caused by an unknown genetic defect.

This report shows for the first time that presumed atypical HDR syndrome may include strabismus, bilateral band keratopathy, and granular retinal pigment epithelium degeneration. Moreover, because retinal involvement may be progressive and lead to severe visual impairment in both eyes in young patients, comprehensive ophthalmic monitoring with funduscopic examination and electroretinography are recommended in patients with HDR syndrome.

REFERENCES