Visual impairment reversal with oral acitretin therapy in keratitis-ichthyosis-deafness (KID) syndrome

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Key words: acitretin; genodermatoses; keratitis-ichthyosis-deafness syndrome; retinoid; therapy.

INTRODUCTION

Keratitis-ichthyosis-deafness (KID) syndrome is a rare genodermatosis with approximately 100 published cases. Although it is classified as an autosomal dominant disorder, more than 90% of cases are caused by sporadic mutations predominantly in gap junction protein β2 (*GJB2*) on chromosome 13q11-q12 (OMIM 148210). *GJB2* encodes connexin 26, a gap junction protein, which plays a role in epithelial differentiation.[1] The characteristic clinical triad includes bilateral sensorineural hearing loss, vascularizing keratitis, and erythrokeratoderma. Treatment with acitretin is reported to clear hyperkeratotic ichthyotic lesions with little effect on vision and hearing.[2,3]

Abbreviations used:

GJB2: gap junction protein β2
KID: keratitis-ichthyosis-deafness

CASE REPORT

A 34-year-old white man with KID syndrome clinically, confirmed by *GJB2* gene analysis missense mutation in codon 50 (D50N), presented to the dermatology clinic. No family members exhibited similar findings. Baseline medications at initial visit included loteprednol 0.5% ophthalmic ointment, half-inch ribbon 4 times daily begun 4 years earlier; triamcinolone 0.1% cream as needed; urea 40% cream; and oral doxycycline, 100 mg twice daily (15-day course for folliculitis). Physical examination revealed hyperkeratotic plaques on his trunk, neck, face, knees, and dorsal hands and feet, and palmoplantar keratoderma. Dystrophic small and absent maxillary teeth were noted. Sensorineural hearing loss was present since childhood. Ophthalmologic examination revealed mild neovascularization and a corrected visual acuity of 20/1200 and 20/800, right and left eye respectively. Acitretin was initiated at a dose of 25 mg once daily. After 2 months of therapy, the patient reported he was newly able to read normal-size text and watch television, which he had not been able to do for several years. At month 4, the patient reported improvement in his hearing with the ability to appreciate music with the use of hearing aids, which he had not been able to do previously with the use of his hearing aids. Side effects at this time included dry lips. At month 7, the patient requested visual acuity testing, which revealed 20/200 visual acuity in both eyes with correction to 20/40 with gas-permeable contact lenses. Punctal plugs were placed by the ophthalmology department at this time and he was fitted for gas-permeable contact lenses. He also experienced near complete resolution of his hyperkeratotic and ichthyotic skin lesions (Figs 1 to 4). The patients' lipids and liver function remained normal during therapy with acitretin. The patient's visual acuity has been maintained for 5 years with minimal side effects and without further progression of his neovascularization.

From the Division of Dermatology, Florida State University College of Medicine.
Funding sources: None.
Conflicts of interest: None declared.
This case was presented as a poster presentation at the 75th Annual Meeting of the American Academy of Dermatology, March 3, 2017 in Orlando, Florida.
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JAAD Case Reports 2017;3:556-8.
2352-5126

http://dx.doi.org/10.1016/j.jdcr.2017.07.021

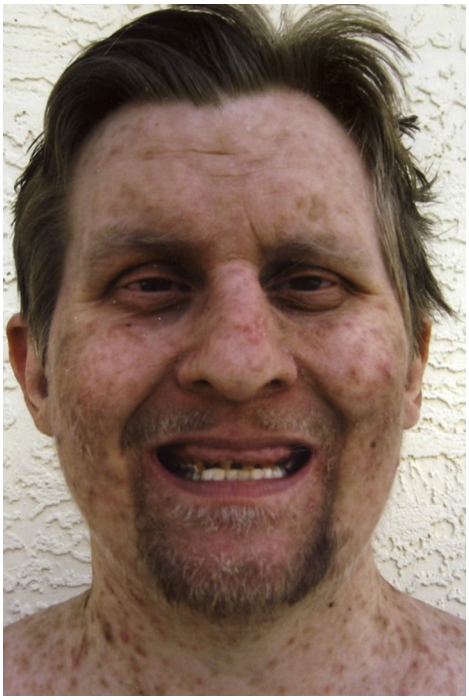

Fig 1. Face, baseline.

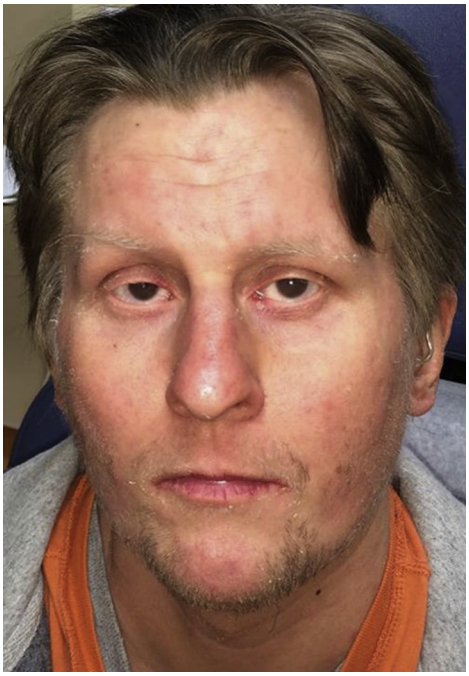

Fig 2. Face after acitretin, month 7.

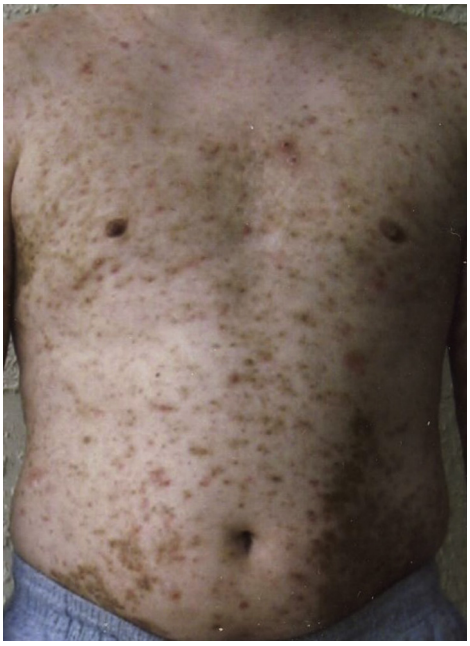

Fig 3. Chest, abdomen, baseline.

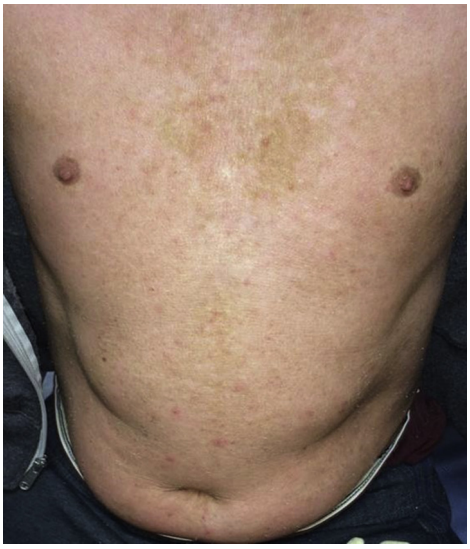

Fig 4. Chest, abdomen, after acitretin month 7.

DISCUSSION

Ocular involvement occurs in 95% of patients with KID syndrome and includes photophobia and blepharitis in early childhood progressing to vascularizing keratitis, neovascularization, and scarring with progressive decline in visual acuity that can lead to blindness. Reported treatments for corneal neovascularization include ophthalmic cyclosporine and corticosteroids.[4] To date, acitretin has shown efficacy in the treatment of cutaneous lesions, whereas other oral retinoids have yielded mixed results.[2,3,5] None of the oral retinoids have reported efficacy for the visual or hearing impairment in KID syndrome, and one case of corneal vascularization with corneal ulcer has been reported with the use of isotretinoin.[5]

Much of the research on the effects of retinoids on connexons has focused on connexin 43, the most widely expressed of the connexin family members.

Ara and colleagues[6] found that retinoic acid increased the amount and phosphorylation of cellular connexins, stabilized connexins within the cellular plasma membrane, and enhanced intercellular gap junction communication. Additionally, several other researchers found enhanced gap junction communication by increasing mRNA and gene product levels via transcriptional regulation with retinoic acid.[7,8] Functional connexin 26 is required to maintain appropriate levels of potassium ions required for conversion of sound waves to electrical impulses within the cochlear cells, and mutated connexin 26 results in channels that constantly leak ions. It is possible that acitretin stabilized and increased the levels of functional wild-type coexpressed connexins, enhancing gap junction communication, resulting in hearing improvement in our patient. The effects of acitretin on epidermal and corneal epithelial connexins may follow a similar mechanistic process in addition to its antiproliferative effects on keratinocytes.

We report this case to highlight the significant impact in quality of life for our patient with subjective hearing improvement and reversal of visual impairment using oral acitretin and corrective gas-permeable contact lenses. Loteprednol 0.5% ophthalmic ointment, started 4 years before his initial visit, was continued throughout acitretin therapy and likely contributed to stabilization of the patients' keratitis. Punctal plugs were placed as a prophylactic measure and likely minimized the adverse ophthalmologic side effects associated with systemic retinoid therapy and may be advisable for patients with KID syndrome who may require prolonged systemic retinoid therapy. Systemic retinoids may also be of benefit in KID syndrome because of the elevated risk of oral and cutaneous squamous cell carcinoma (10% to 20% of patients); however, because of the rarity of the disease and resultant paucity of literature, this is only speculative at present.[9] Our case is unique in that improvement in visual acuity with the use of acitretin or other systemic retinoids, to our knowledge, has yet to be reported in the literature.

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