CASE REPORT

Reversible retinopathy associated with oral deferasirox therapy

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SUMMARY

A 17-year-old girl with a history of sickle cell anaemia undergoing chronic blood transfusions and iron-chelation therapy presented for multiple ophthalmic examinations. During treatment with deferoxamine, her examination remained stable but 2 years after changing to deferasirox she presented with decreased visual acuity and only mild fundusoscopic changes. Marked electrophysiological abnormalities were also evident. After cessation of deferasirox, her visual acuity improved and electrophysiological responses improved. No prior reports of deferasirox-related retinopathy are available. We suggest that oral deferasirox caused a reversible retinopathy in our patient and clinicians be aware of this entity.

BACKGROUND

Red blood cell transfusions are an important therapy for various medical conditions. Chronic transfusions can induce morbidity as sequelae of iron overload. Chelating agents are vital in removing excess iron and avoiding toxicity. Only two agents are used routinely: deferoxamine and deferasirox. Deferoxamine is a siderophore that has

been commercially available for over 30 years.¹ Deferasirox is a highly protein-bound synthetic chelator that became available in 2005.² Known adverse effects of deferoxamine include reduced skeletal growth and retinopathy.¹ Preclinical and clinical trials of deferasirox report that it is well tolerated and lacks ophthalmic toxicity²; however, recent reports have documented over 4000 deaths due to deferasirox, especially when the dose exceeds 40 mg/kg/per day.³ We present a case of reversible deferasirox-related retinopathy that has previously not been described.

CASE PRESENTATION

A 17-year-old African-American girl with sickle cell anaemia (Hb SS disease) initially presented for ophthalmic examinations at age 9. She was undergoing bimonthly red blood cell transfusions after a non-debilitating left anterior cerebral occlusion at age 7. From age 9 until 11, she underwent chelation therapy with low-dose post-transfusion intravenous deferoxamine 15 mg/kg/h and had two annual ophthalmic examinations at which she achieved best corrected visual acuities of 20/40 in the right eye

Figure 1 Colour fundus photographs revealing mild macular pigment abnormalities.

Figure 2 Optical coherence tomography with normal foveal architecture.

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Figure 3 Fluorescein angiography without vascular filling abnormality.

due to refractive amblyopia and 20/20 in the left eye, and had no retinopathy in either eye.

At age 12, intravenous deferoxamine was substituted with oral deferasirox 1000 mg/day (22 mg/kg/day) to reduce risk of skeletal growth deficiencies. Two annual examinations remained stable and an electroretinogram was performed 2 years after cessation of deferoxamine to evaluate for any subclinical signs of retinal toxicity and revealed mildly attenuated rod function in the right eye. The dosage of deferasirox was lowered to 500 mg/day (11 mg/kg/day) and two subsequent annual examinations were unremarkable.

Four years after switching to deferasirox, she reported decreased vision in the left eye. At that time, visual acuity was 20/50 in the right eye, finger counting in the left eye. No relative afferent pupillary defect was present. Mild macular

pigmentary changes were evident in both eyes without evidence of optic nerve or retinal vascular disease (figure 1).

INVESTIGATIONS

Optical coherence tomography revealed normal foveal architecture (figure 2). Fluorescein angiography and indocyanine-green angiography were without vascular filling abnormalities (figure 3). Fundus autofluorescence revealed very mild retinal pigment epithelium dropout in both eyes (figure 4).

DIFFERENTIAL DIAGNOSIS

The visual loss in this case is marked by electrophysiological depression and lack of anatomic or vascular abnormality. The temporal relationship of visual loss and electrophysiological depression correlates with cumulative deferasirox use.

Figure 4 Fundus autofluorescence with mild retinal pigment epithelium dropout.

Figure 5 ERG with decrease in both rod and cone function and Goldmann visual fields with central scotomas in both eyes.

TREATMENT

Deferasirox therapy was discontinued.

OUTCOME AND FOLLOW-UP

Repeat evaluation 2 weeks after discontinuation measured visual acuities of 20/40 in the right eye and 20/300 in the left eye. ERG revealed a decrease in both rod and cone function of approximately 30% from baseline and Goldmann visual fields revealed central scotomas in both eyes (figure 5). Five months after discontinuation, visual acuities continued to improve and measured 20/50 in the right eye and 20/30 in the left eye. Repeat ERG revealed improved electrophysiological responses in both eyes and Goldmann visual fields revealed slight improvement of scotomas in both eyes (figure 6). One year after discontinuation, visual acuities measured 20/40 in the right eye and 20/20 in the left eye.

DISCUSSION

No prior reports of deferasirox-related retinopathy exist. While deferoxamine-related retinopathy is a recognised clinical entity, its pathophysiology remains unclear.⁴ It is thought that deferasirox-iron complexes form and induce mitochondrial calcifications. These calcifications then induce a loss of RPE microvilli and subsequently a thickening of Bruch's layer, ultimately impairing RPE function. Alternatively, a trace mineral depletion can result from chelator therapy which then promotes oxidative stress in the RPE cell membranes. This ultimately impairs neurotransmission.⁴ Some reports indicate visual loss can improve after discontinuation, while others suggest it is irreversible.^{5–7} Our patient demonstrated reversible retinopathy strongly correlated to deferasirox usage with adequate ancillary testing to rule out other possible causes. Additional reports on deferasirox-related retinopathies can contribute greatly to the understanding of this entity.

Figure 6 Repeat ERG with improved electrophysiological responses in both eyes and Goldmann visual fields with mild improvement of scotomas.

Learning points

- Clinicians using iron-chelation therapy should be aware of potential retinopathy that exists with both deferasirox and deferoxamine.
- The clinical course of iron-chelator retinopathy remains unclear and additional cases with electrophysiological testing can elucidate the prognosis.
- No established guidelines for ophthalmic screening examination exist for patients on iron-chelation treatment. Additional case reports of these entities can help establish guidelines for ophthalmic examination and consultations.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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Competing interests None.

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