Bilateral maculopathy in a thalassemia patient on iron chelation therapy: a case report

Maculopatia bilateral em paciente com talassemia em terapia quelante de ferro: relato de caso

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ABSTRACT

A 10-year-old Malay girl with underlying HbE/beta-thalassemia, on regular blood transfusion and deferoxamine iron chelation therapy, presented with two-month history of bilateral blurring of vision. On examination, her vision was 6/36 both eyes. Other optic nerve functions were normal. Anterior segment examination of both eyes was unremarkable. Fundus examination of both eyes revealed dull foveal reflex. Optical coherence tomography of both maculae showed increased central subfield thickness. Fundus fluorescence angiography showed patchy hypofluorescence over macular region for both eyes and late staining, indicating retinal pigment epithelium anomalies. A diagnosis of iron-chelation-therapy-related bilateral maculopathy was made. Patient was co-managed with pediatric hematology team to adjust the dose of deferoxamine, and was given three monthly appointments to monitor the progression of maculopathy at the ophthalmology clinic. However patient defaulted ophthalmology follow-up after the first visit.

RESUMO

Uma menina malaia de 10 anos de idade com doença de base- B/beta-talassemia, em transfusão de sangue regular e terapia quelante de ferro deferoxamina, apresentou história de dois meses de visão turva bilateral. Ao exame, sua visão era de 6/36 em ambos os olhos. Outras funções do nervo óptico estavam normais. O exame do segmento anterior de ambos os olhos foi normal. Exame do fundo de ambos os olhos revelou reflexo foveal opaco. A tomografia de coerência óptica de ambas as máculas mostrou aumento da espessura do subcampo central. A angiografia de fluorescência do fundo mostrou hipofluorescência irregular sobre a região macular de ambos os olhos e coloração tardia, indicando anomalias de epitélio pigmentar da retina. Um diagnóstico de maculopatia bilateral relacionada à terapia quelante de ferro foi feito. A paciente foi avaliada em conjunto com a equipe de hematologia pediátrica para ajustar a dose de deferoxamina, e foram oferecidas três consultas mensais na clínica oftalmológica, para monitorar a progressão da maculopatia. No entanto, ela não compareceu para acompanhamento oftalmológico após a primeira visita.

INTRODUCTION

Thalassemia is an autosomal recessive inherited hemoglobin disorder. Based on the types of globin defects, the thalassemia can be divided into alpha and beta. A beta-thalassemia (β-thalassemia) occurs if a gene or genes related to the beta-globin proteins are involved and result in deficiency of beta-globin chain synthesis.[1] HbE is an abnormal beta hemoglobin variant, resulting in a structurally abnormal hemoglobin molecule causing limited erythropoiesis, as well as associated with shortening of red cell survival. Patients usually required regular blood transfusion to maintain the optimum amount of hemoglobin in the body. Frequent blood transfusion can lead to iron deposition in the retina. The iron complexes can enter the retinal pigment epithelium (RPE) cells by binding to the surface transferrin receptors, which are associated with the cytoskeleton.[2] When the excess iron complexes are transported into the cells, the hydroxyl radicals are released and damage the cells. Long-term therapies with iron chelation agents (ICA) can cause an unwanted adverse effect to the eyes. Hence, we report a case of a HbE/β-thalassemia patient on iron chelation with deferoxamine presenting ocular symptoms secondary to maculopathy.

Patient and her parents have consented throughout the whole process of collecting data, and producing the manuscript for publication. Verbal consent obtained.

CASE REPORT

A 10-year-old Malay girl presented with both eye blurring of vision for 2 months. It was associated with central scotoma. Patient is diagnosed as HbE/beta- thalassemia since the age of 2 years, and is currently on regular monthly blood transfusion with the ICA deferoxamine.

Upon initial examination, vision of both eyes was 6/36. Other optic nerve functions were tested as well. There was no relative afferent pupillary defect. The light brightness and red desaturation were normal on both eyes. The color vision test using Ishihara pseudoisochromatic plates was normal. The anterior segment examination of both eyes was normal. Fundus examination of both eyes reviewed dull foveal reflex. No submacular fluid noted. The optic disc was normal with cup to disc ratio of 0.5. All retinal vessels appeared to be normal. Peripheral retina was normal with no abnormal pigmentation. The intraocular pressure was normal in both eyes. Optical coherence tomography (OCT) of the macula was done. There was a slightly increased central subfield thickness of both eyes, right eye at 276 µm and left eye at 265 µm (Figures 1 and 2). There was no intraretinal or subretinal accumulation of fluid. The RPE and inner segment and outer segment (ISOS) junction of the photoreceptors appeared intact. Parafoveal parameters were normal. Optical coherence tomography of optic nerve head was normal for both eyes. Fundus fluorescence angiography (FFA) of the eyes was performed. The angiogram showed early patchy hypofluorescence, followed by late staining, indicating RPE dysfunction as the main cause of increased macular thickness and decreased vision. Patient was co-managed with pediatric hematological team. A diagnosis of ICA-related maculopathy was made. Pediatric team planned for dose adjustment of the ICA to minimize further macular damage. On ocular part, patient was treated conservatively in a 3-month follow-up.

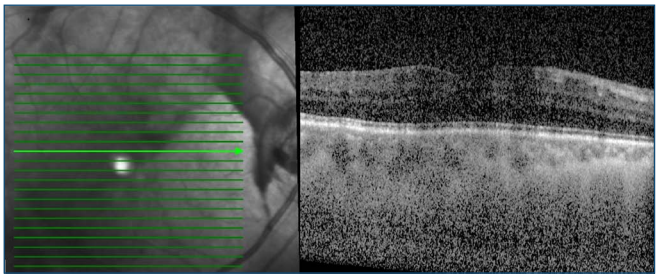

Figure 1. Right eye-- Increased central retinal thickness on OCT of macula with intraretinal fluid

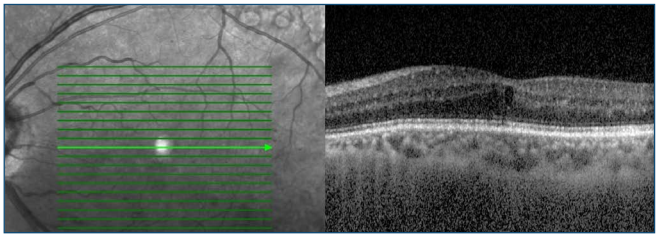

Figure 2. Left eye—Intraretinal fluid seen on OCT of macula

Unfortunately, we were unable to monitor the progression of her eyes, since she defaulted ophthalmological follow-up.

DISCUSSION

One of the mainstay treatments in beta-thalassemia patients is blood transfusion. However chronic blood transfusion can lead to excessive deposition of iron particles in all tissues including the eye. The iron complexes can enter the RPE cells by binding to the surface transferrin receptors. When the excess iron complexes are transported into the cells, the hydroxyl radicals are released through the Fenton reaction. These free radicals are harmful and toxic to the cells, since they can destroy the cell protein, lipid, DNA, as well as disrupt the blood retinal barrier.

Some researchers found the ferritin particles were mainly accumulated in the Muller and RPE cells, which can cause cell degeneration.[3] The accumulation of iron in retinal cells can even lead to iron-induced maculopathy with atrophy of RPE.

Iron chelation therapy is another important treatment in HbE/beta-thalassemia patients nowadays, especially for those under regular transfusions. The ICA help removing the excess harmful iron particles from the body, and therefore lower the risk of iron-related ocular toxicity. RPE degeneration and mottling in β-thalassemia major patients who received high-dose deferoxamine therapy has been reported.[4] Although excess iron can be removed from the body by ICA, these therapies have the potential to cause ocular adverse effects, such as pigmentary maculopathy, pigmentary retinopathy and degeneration of the RPE. A case of deferasirox-related maculopathy with outer macular thinning, and disruption of the inner/outer segment junction at the parafoveal regions in both eyes under the OCT has been reported. Although ICA-related ocular toxicity has been reported in a number of studies and case reports, the incidence rate of toxicity remains uncertain. Baath *et al*. conducted a 10- year study with 84 pediatric patients, who had received the regular deferoxamine treatment, and aimed to find out the incidence of the drug-related ocular toxicity. Surprisingly, the ocular adverse effect was reported as low as 1%, with presence of reduced central visual acuity and RPE changes.[5] Although the pathophysiology of the ICA-related retinopathy has been investigated for many years, it remains unclear. Yet, the direct toxic effect from the excessive iron tissue deposition cannot be excluded.[6] In our patient, there was increased central subfield thickness on OCT and late staining in FFA. These may indicate RPE dysfunction due to the use of ICA causing accumulation of subtle intraretinal fluid, which subsequently affected the central vision.

Currently there is no standard therapy for ICA-induced maculopathy other than drug discontinuation or dose reduction. Several reports in the literature suggested dose of deferoxamine of not more than 50 mg/kg can aid reduce the risk of maculopathy and retinopathy.[7] In this patient, the pediatric team adjusted the dose according to patient's hepatic iron concentration at its minimal, to balance between iron overload and progression of maculopathy. Even though there are tests to confirm ICA-toxicity, they were not ordered, since the patient is a child and more invasive tests were not recommended by managing team. Thus, the diagnosis was made based on clinical presentation. Presence of subtle maculopathy should be followed up for 3 to 6 months and any dystrophy-like changes at the macula should indicate discontinuation of the drug to prevent progression, and possible risk of permanent visual loss.

REFERENCES

1. Thein SL. Genetic modifiers of beta-thalassemia. Haematologica. 2005;90(5):649-60.
2. Simon S, Athanasiov PA, Jain R, Raymond G, Gilhotra JS. Desferrioxamine-related ocular toxicity: a case report. Indian J Ophthalmol. 2012;60(4):315-7.
3. Dunaief JL, Richa C, Franks EP, Schultze RL, Aleman TS, Schenck JF, et al. Macular degeneration in a patient with aceruloplasminemia, a disease associated with retinal iron overload. Ophthalmology. 2005;112(6):1062-5.
4. Taneja R, Malik P, Sharma M, Agarwal MC. Multiple transfused thalassemia major: ocular manifestations in a hospital-based population. Indian J Ophthalmol. 2010;58(2):125-30.
5. Klettner A, Koinzer S, Waetzig V, Herdegen T, Roider J. Deferoxamine mesylate is toxic for retinal pigment epithelium cells in vitro, and its toxicity is mediated by p38. Cutan Ocul Toxicol. 2010;29(2):122-9.
6. Hidajat RR, McLay JL, Goode DH, Spearing RL. EOG as a monitor of desferrioxamine retinal toxicity. Doc Ophthalmol. 2004;109(3):273-8.
7. Brittenham GM. Iron-chelating therapy for transfusional iron overload. N Engl J Med. 2011;364(2):146-56.