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Retinal abnormalities in β -thalassemia major

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Abstract

Patients with beta (β)-thalassemia (β -TM: thalassemia major, β -TI: thalassemia intermedia) have a variety of complications that may affect all organs, including the eye. Ocular abnormalities include retinal pigment epithelium degeneration, angioid streaks, venous tortuosity, night blindness, visual field defects, decreased visual acuity, color vision abnormalities, and acute visual loss. Patients with β -TM are transfusion dependent and require iron chelation therapy (ICT) in order to survive. Retinal degeneration may result from either retinal iron accumulation from transfusion-induced iron overload or retinal toxicity induced by ICT. Some who were never treated with ICT exhibited retinopathy, and others receiving ICT had chelator-induced retinopathy. We will focus on retinal abnormalities present in individuals with β -TM viewed in light of new findings on the mechanisms and manifestations of retinal iron toxicity.

Keywords

Beta-thalassemia major; Iron; Iron-overload, Deferrioxamine retinopathy; Deferiprone; Heparin; Pseudoxanthoma elasticum; PXE-like syndrome

1. Introduction

Normal hemoglobin consists of tetramers composed of two homo-dimers. Adult (HbA) and fetal (HbF) hemoglobins consist of two alpha-chains combined with beta (HbA, $\alpha_2\beta_2$), delta (HbA₂, $\alpha_2\delta_2$), or gamma chains (HbF, $\alpha_2\gamma_2$). Hemoglobinopathies are disorders caused by mutations in specific globin genes such as α or β , leading to ineffective erythropoiesis. ^{17, 95} β -thalassemia is an autosomal recessive disorder caused by defective β globin production. In its severe form, affected individuals require regular blood transfusions to survive.

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9. Disclosure

JLD receives research funding from ApoPharma, maker of deferiprone. He also has a patent pending on deferiprone for treatment of AMD.

Chronic blood transfusion therapy prolongs their lives, but humans cannot actively excrete iron. Thus, iron-rich blood transfusions cause iron overload. This leads to toxic accumulation of iron in the liver, spleen, endocrine organs, myocardium, and, potentially, the eye.¹⁴ Fortunately, iron overload may be controlled with chelating agents capable of binding iron and promoting its excretion. Deferrioxamine (delivered by subcutaneous or intravenous infusion) and two oral iron chelators, deferiprone and deferasirox, are approved for human use.²⁴ Various studies have cited ophthalmologic changes in patients with thalassemia. This review will focus on retinal manifestations that occur as a result of the disease and the iron chelator-induced retinopathy. Changes in the fundus, in the form of retinal pigment epithelium (RPE) mottling, RPE degeneration, and angioid streaks are reported. Furthermore, we will discuss the role of matriptase-2 (Tmprss6), a serine protease expressed in the retina, and how its pharmacologic modulation could reduce iron burden systemically and within the retina.

1.1 β -thalassemia

β -thalassemia, an autosomal recessive hemoglobinopathy, is prevalent worldwide. The Mediterranean, Middle East, Central Asia, Transcaucasus, Indian subcontinent, and the Far East have populations with the highest prevalence. Additionally, it is rather common in individuals of African descent. Cyprus (14%), Sardinia (12%), and South East Asia have the highest prevalence of β -thalassemia.⁹⁴ Presumably, the selective pressure from *Plasmodium falciparum* malaria led to the high gene frequency of this disorder in these regions. Nevertheless, population migration has led to β -thalassemia in Northern Europe, Caribbean, North and South America, and Australia.¹⁷

Disease severity is determined by the degree of β -globin chain production. Patients with thalassemia major have markedly diminished β -globin chain production and have the most severe phenotype, requiring regular blood transfusions in order to survive. Patients with thalassemia intermedia have more β -globin chain production than those with thalassemia major, reducing the severity of the disease, but sometimes need blood transfusions. The result of this defective β -globin chain production is an imbalanced globin chain production with excess α -chains. The abnormal red blood cells suffer premature destruction from oxidative damage of the cell membrane in the bone marrow.^{17, 65}

2. Retinal abnormalities in β -thalassemia major and intermedia

2.1 Overview

Individuals suffering from β -TM (thalassemia major) and β -TI (thalassemia intermedia) may develop retinal pathology. The retinal pathologies can be separated into two groups: 1) pseudoxanthoma (PXE)-like retinal abnormalities and 2) non-PXE-like retinal abnormalities. PXE is a hereditary disease caused by mutations in the *ABCC6* (ATP-binding cassette, subfamily C (CFTR/MRP), member 6) gene on chromosome 16. The *ABCC6* gene encodes a protein called multidrug resistance associated protein 6, which is found in the liver, kidneys, stomach, skin, blood vessels, and eyes.³³ The *ABCC6* gene mutation is not seen in β -thalassemic individuals; however, Martin and colleagues demonstrated that erythroid transcription factor nuclear factor-E2 causes a gradual downregulation of *ABCC6*

gene expression and protein levels in a β -thalassemia mouse model. ^{12, 66} There was a 25% reduction in the levels of Abcc6 protein in the β -thalassemia mouse model at age 10 months. ⁶⁶ Thus, β -thalassemic patients could have diminished *ABCC6* gene expression leading to the PXE-like syndrome. ^{12, 63}

PXE is characterized by calcium mineralization of elastic fibers (elastin). ³³ Calcium and other minerals are deposited in elastin in the blood vessels, skin, and Bruch's membrane under the retinal pigment epithelial cells. ^{33, 37} Various studies from the early 1990s demonstrated similar ocular manifestations in β -thalassemia and PXE. ^{1, 6, 12, 15, 51} Aessopos and colleagues established the terms "PXE-like-lesion" and "PXE-like syndrome" to help differentiate PXE from acquired PXE-like syndrome findings. ⁵ PXE-like syndrome refers to the following retinal abnormalities: angioid streaks, peau d'orange, and optic disc drusen development. Retinal venous tortuosity (RVT) is considered the primary non-PXE like retinal abnormality found in β -thalassemia. ¹²

Some β -thalassemia-associated retinal pathologies cited in the literature include retinal pigment epithelium (RPE) degeneration, RPE mottling, angioid streaks, retinal vessel tortuosity, retinal hemorrhages, retinal edema, pseudo-papillitis, and macular scarring. ^{9, 36, 76, 84, 86} We performed a meta-analysis on five cross-sectional studies by identifying common ocular findings among the papers and calculating prevalence values (Table 1).

We identified retinal abnormalities in β -TM patients associated with transfusional iron overload in the literature. These patients had not received iron chelation therapy (ICT). RPE mottling, retinal venous tortuosity, and angioid streaks occurred in this subset of individuals (Table 2). As a point of clarification, RPE degeneration was described as early hyperfluorescence on fluorescein angiography. ³⁶ Taher and colleagues defined RPE degeneration as "salt and pepper" appearance in the macula or pigmentation in the peripheral retina. ⁸⁶ RPE mottling was also described as hyper- and hypo-autofluorescence shown on fundus autofluorescence (FAF) imaging. ^{80, 89}

2.2. Pseudoxanthoma (PXE)-like retinal abnormalities

2.2.1. Peau d'orange—Peau d'orange refers to small confluent dark yellowish lesions at the level of the retinal pigment epithelium. ³⁷ This finding often precedes angioid streaks. Initially, calcification of the Bruch's membrane occurs at the posterior pole and spreads centrifugally. This is associated with the peau d'orange appearance. Barteselli and colleagues found peau d'orange was the most frequent finding in β -thalassemic patients. ¹²

2.2.2. Angioid Streaks—"Angioid streak" is a retinal pathology that results from structural changes in the Bruch's membrane underlying the RPE. Histopathologic findings include irregular crack-like dehiscences in Bruch's membrane that are associated with atrophic degeneration of the overlying RPE. ^{12, 41, 61} Angioid streaks are associated with pseudoxanthoma elasticum, Paget's disease of bone, acromegaly, Ehlers-Danlos syndrome, diabetes mellitus, sickle cell anemia and β -thalassemia. ^{2, 3, 4, 6, 12, 21, 41, 42, 61, 62}

Angioid streaks are usually an asymptomatic finding on retinal examination. Angioid streaks become problematic when the lesion extends towards the foveola or develops complications such as macular choroidal neovascularization (CNV) and traumatic Bruch's membrane rupture. ^{6, 12, 41, 42, 61} Individuals who have angioid streaks and have traumatic brain injury have an increased likelihood of visual damage because the Bruch's membrane is weakened by the angioid streaks. ^{41, 47} Ultimately, CNV, the most serious complication of angioid streaks, can cause severe loss of visual acuity. ⁴¹

2.2.3. Optic nerve head (ONH) drusen—Drusen deposition in the optic nerve head is found with increased prevalence in PXE patients. This has also been noted in patients with β -thalassemia.

2.3. Non-PXE-like retinal abnormalities

2.3.1. Retinal venous tortuosity—Retinal venous tortuosity (RVT) has been observed in β -TM individuals. ⁸⁴ Chronically anemic patients demonstrated an inverse relationship between hematocrit and RVT. ⁷ RVT increases with age in β -thalassemics when compared to age-matched non-thalassemics. The mild and chronic anemia that occurs in between transfusions results in tissue hypoxia leading to RVT. ⁵⁶ Additionally, splenectomy correlates with increased vascular tortuosity, potentially because of increased thrombotic risk post-splenectomy. ¹²

2.4. Conclusions

β -thalassemia and PXE share similar ocular fundus changes. This suggests a similar PXE-like elastin calcification may occur in β -thalassemia. Importantly, PXE and β -thalassemia share the following retinal findings: peau d'orange, angioid streaks, and ONH drusen. Comet lesions, common to PXE, have not been found with β -thalassemia. Patients with β -TI have a higher risk of developing PXE-like retinal abnormalities than β -TM patients.

3. Iron and the retina

3.1 Overview

Iron toxicity from multiple blood transfusions may contribute to β -thalassemia retinopathy. In general, iron is an important component of many metabolic processes, but appropriate regulation is necessary in order to prevent toxicity. ^{81, 97} In the retina, iron is needed in the visual phototransduction cascade for isomerohydrolase activity carried out by the RPE65 protein in the retinal pigment epithelium. ⁶⁸ Mouse models reveal that systemic iron overload through intraperitoneal injections can lead to increased iron levels in the RPE. ¹⁰⁰ Iron in the retina becomes problematic when ferrous iron (Fe^{2+}), which can generate hydroxyl radicals from hydrogen peroxide in the Fenton reaction, causes oxidative damage to the retina and RPE. ^{43, 70} Therefore, there are regulatory mechanisms for the import and export of iron from the eye. Iron in the systemic circulation is deterred from entering the retina by the intercellular tight junctions of the neuroretinal vasculature and RPE. ⁸¹ Moreover the cells comprising these barriers regulate its import. Once in the retina ferric iron (Fe^{3+}) can bind to transferrin, an iron-binding protein that is abundant in the vitreous and aqueous humors. ^{45, 82} Iron export from retinal cells is facilitated by multicopper

ferroxidases, such as ceruloplasmin (Cp) and its homolog hephaestin (Heph).⁹⁶ Their function in iron export has been highlighted in mice with combined deficiency of Cp and Heph leading to age-dependent iron accumulation in the retina and RPE resulting in degeneration.^{30, 49} The RPE becomes hypertrophic, autofluorescent, and dysplastic. Ferroportin, the only known mammalian iron exporter, works in cooperation with Cp and Heph. Moreover, ferroportin is also expressed in the mouse retina and RPE.⁴⁸

Retinal pathologies in thalassemic patients notably involve the retinal pigment epithelium (RPE).^{9, 36, 84, 86} The RPE has been hypothesized as the site of increased iron deposition in β -TM patients.⁸⁴ A post-mortem β -TM eye exhibited iron deposits with Perls stain in the non-pigmented ciliary epithelium, ciliary muscle, choroidal stromal cells, sclera, peripheral retina, and occasionally in the photoreceptor layer and RPE.⁷⁴ Increased RPE iron deposition and subsequent iron overload has been correlated with RPE damage and degeneration.^{28, 29, 30, 43, 45, 48, 49, 52, 81, 97} Several lines of evidence have implicated the RPE as the location of iron accumulation and damage in age-related macular degeneration (AMD).^{52, 81, 97}

3.2 RPE hypertrophy

Ceruloplasmin/hephaestin double knockout mice accumulated iron in the RPE that led to RPE hyperplasia and hypertrophy in mice that survived until 12 to 13 months.⁴³ The RPE stress response is characterized by RPE de-differentiation and hypertrophy. A similar stress response was observed in RPE cells of mice with conditional knockout of the mitochondrial RNA polymerase, which had activation of the AKT/ mammalian target of rapamycin (AKT/ mTOR) pathway.⁹⁹ The mTOR pathway allows the RPE cell to prolong its survival at the cost of epithelial characteristics leading to disrupted interactions with the surrounding photoreceptor cells. In the *postmortem* eye from a patient with β -TM, the RPE cells were enlarged and projected into the subretinal space. Additionally, transmission electron microscopy demonstrated RPE cell structural variations: swollen mitochondria, thickened Bruch's membrane under the degenerated or depigmented RPE cells, and loss of basal plasma membrane infolding. It is important to note that β -TM, transfusional iron overload, DFO toxicity, or both could have caused this pathology.⁷⁴

4. Iron chelation therapy

4.1 Overview of chelation therapy

Iron overload is unavoidable in patients who undergo life-long hypertransfusion therapy. Each unit of transfused blood introduces 200 to 250 mg of elemental iron into the body. Since iron cannot be actively excreted and is poorly used in individuals with ineffective erythropoiesis secondary to β -TM, excess iron is deposited in the viscera (i.e. liver, heart, pancreas, and possibly, eye).¹⁷ Patients who receive transfusions have an average intake of 8 to 16 mg of elemental iron per day, as opposed to the normal intake of 1-to 2-mg of dietary iron per day. Furthermore, accelerated oral iron uptake in thalassemic patients contributes to the total iron overload. Iron chelation therapy (ICT) is necessary to reduce the iron burden.⁶⁵ ICT is initiated before age 6. Once initiated, ICT must be rigorously followed and frequently monitored in order to be effective and prevent complications such

as heart failure and endocrine dysfunction (e.g. pancreatic failure, infertility). Furthermore, several studies have shown in mouse models of retinal iron overload that ICT may slow progression of retinal damage.⁶⁷ Table 3 summarizes the advantages and disadvantages of the current clinically available iron chelators.

4.2 Iron chelation (IV and subcutaneous): Deferrioxamine (DFO)

Deferrioxamine mesylate (DFO), an iron-chelating drug, is used to treat transfusion-related hemochromatosis. DFO was the first ICT that effectively prolonged the survival of β -thalassemic patients from the second decade of life to a normal lifespan. The side effects of DFO are numerous and include bone dysplasia, auditory toxicity, and retinal toxicity.

4.3 DFO ocular toxicity

DFO-induced ocular toxicity includes symptoms of night blindness, impaired color vision, impaired visual field, reduced visual acuity, and RPE changes (i.e. macular or peripheral pigmentary degeneration).^{11, 22, 25, 27, 38, 40, 64, 80, 89, 91} The standard dosage of DFO in patients ranges from 25-50 mg/kg/d. 50mg/kg/d was noted to be the upper limit before ocular and ototoxicity presents.²² The first study documenting ocular toxicity indicated 100 mg/kg/d DFO as a dose that would cause toxicity.²⁵

DFO retinopathy has been assigned specific criteria.⁹¹ We summarize 29 articles related to DFO retinopathy in Table 4. Intravenous DFO seems to present a greater risk of retinal toxicity compared to subcutaneous and intramuscular.¹¹ In studies from 1983 to 2008, investigators performed retinal examinations utilizing dilated fundus examinations (DFE), fluorescein angiogram (FA), electro-retinography (ERG), electro-oculogram (EOG), and visual evoked potentials (VEP). Studies after 2008 utilized spectral domain optical coherence tomography (SD-OCT) and fundus autofluorescence (FAF) (Table 4). Several papers discussed the phenomenon of DFO retinopathy reversibility.^{11, 13, 18, 25, 27} In some cases, the cessation of DFO led to a partial or complete reversal of visual symptoms and retinal findings. DFO related ocular toxicity indicates the need for ophthalmic examinations in individuals on DFO therapy.^{11, 50}

The RPE undergoes pathologic change in DFO retinopathy.^{89, 91, 92, 98} Abnormal fluorescence on FA or FAF provide a gauge of retinal and RPE damage.^{50, 92} Moreover, Viola and colleagues indicated that FAF imaging is a more sensitive modality than ophthalmoscopy for detecting RPE abnormalities.⁹² Recent studies have indicated that several stages of maculopathy exist and may influence visual outcomes if early intervention is initiated. Please refer to section 5 for a more detailed discussion on disease management and recommendations.

4.4 Iron chelation (Oral): Deferiprone and Deferasirox

Deferiprone (DFP) and deferasirox are two oral iron chelators that provide an alternative to deferrioxamine ICT (Table 3). DFP has been shown in various murine studies to provide effective retinal iron chelation. This is because of DFP's ability to cross the blood-retinal-barrier and chelate intracellular iron with no evidence of retinal toxicity.^{23, 34, 81, 83} Approximately 1% of patients have severe side effects, specifically reversible

agranulocytosis and neutropenia. Deferasirox provides effective systemic iron chelation, but there is no evidence of retinal penetration.

4.5 Deferiprone: a potential retinal protective iron chelator

Deferiprone (DFP) can be administered orally with fewer systemic side effects than DFO, most of which can be prevented or reversed by careful monitoring.^{34, 81} Ceruloplasmin (Cp) and its homolog Heph (hephaestin) are two ferroxidases that regulate iron. When Cp and Heph are deficient, iron overload occurs within the retina.⁸¹ Oral DFP administered to iron overloaded Cp/Heph deficient mice effectively decreased retinal iron and oxidative stress levels.⁴⁶ Moreover, DFP demonstrated significant protection of the saturated rod and cone-b waves in ERG studies in mice treated with sodium iodate (NaIO₃) alone and cotreated with NaIO₃ and DFP.⁴⁴ Furthermore, oral DFP was shown to protect the retina against NaIO₃ induced oxidative stress, as indicated by reduced expression of the stress-related gene heme-oxygenase-1 and the complement gene C3.⁴⁴ Mice deficient in the iron regulatory hormone hepcidin (*Hepc*) develop systemic and retinal iron overload over time. DFP treatment of *Hepc* deficient mice protected against RPE depigmentation and autofluorescence, preserved RPE and photoreceptor morphology, and preserved ERG rod a- and b- and cone b-wave amplitudes.⁸³ Finally, in non-iron-overloaded pathologies such as light damage-induced photoreceptor death, DFP proved to be protective.⁸²

Two studies documented RPE degeneration associated with deferiprone use;^{86, 87} however, it was not possible to determine whether the degeneration was caused by iron toxicity, toxicity from prior DFO treatment, or any potential deferiprone toxicity.

5. Disease management

The management of β -TM requires chronic hypertransfusion therapy and iron chelation in order to permit prolonged survival.^{17, 65} As mentioned earlier, iron chelation therapy is necessary to counteract the iron overload that results from the hypertransfusion regiment. The iron overload caused by the transfusion therapy and the iron chelator-induced toxicity both increase the need for thalassemic patients to undergo regular ophthalmic evaluations.^{9, 31, 56, 57}

5.1 Retinal Abnormalities

Adverse retinal effects may occur as a result of the iron chelators or the disease itself and include the following: retinal pigment epithelium (RPE) degeneration, RPE mottling, retinal venous tortuosity, and vitreoretinal hemorrhages. Thalassemic patients may present with decreased visual acuity, color vision anomalies, night blindness, cataracts, visual field defects, and optic neuropathy.^{9, 31, 36, 76, 84, 86, 87} The ophthalmic evaluation may include a dilated fundus examination (DFE), fluorescein dye retinal angiography, indocyanine green angiography, optical coherence tomography, and fundus autofluorescence.^{40, 50, 53, 64, 76, 80, 91, 92, 98} Furthermore, monitoring of retinal function with ERG has been useful in β -TM patients who have nine or more years of transfusions unprotected by iron chelation therapy.⁵⁷

Spectral domain- optical coherence tomography (SD-OCT), a non-invasive technique that uses low coherence light reflected by the retinal tissue,⁸ can measure retinal nerve fiber layer (RNFL) thickness and provide a basic, noninvasive histological view of the retina.^{8, 31} Recent studies have evaluated β -TM children RNFL thickness values with SD-OCT, and determined that β -thalassemics have a thinner RNFL in all quadrants when compared to children with iron deficiency anemia and normal non-anemic children.⁸

Microperimetry records the patient's sensitivity to a visual stimulus and correlates that to the structure of the retina at the location of the stimulus.⁹⁰ Gelman et al demonstrated an overall decreased macular sensitivity and attenuation in the inferotemporal macula.^{39, 40} The use of this advanced visual field technology is not widely used in the assessment of β -thalassemic patients with DFO induced retinopathy. When more evidence is available, microperimetry might play an important role in the ophthalmic evaluation of these individuals.

5.2. Iron chelator induced retinopathy: staging and assessment

DFO retinopathy is classically described as a “bull's eye maculopathy” on retinal examination.^{40, 74} The advent of more sophisticated and refined ophthalmic technologies has made it possible to detect subtle retinal changes primarily attributed to DFO toxicity. The retinal changes occur at the RPE-Bruch's membrane-photoreceptor complex.^{91, 92} We will focus on recent studies and summarize their recommendations.

The confocal scanning laser ophthalmoscope (cSLO) allows practitioners to evaluate RPE lipofuscin accumulation. Lipofuscin is a non-degradable end product of photoreceptor outer segment breakdown and the bisretinoid A2E. This end product has autofluorescent properties and builds up in the RPE. The SLO takes advantage of this lipofuscin deposition by detecting changes in fundus autofluorescence (FAF). FAF has been established as a superior non-invasive prognostic tool that can detect early changes of retinal toxicity.^{26, 54, 55, 60, 75, 85, 93} Viola et al established four phenotypic patterns of abnormal FAF: minimal change, focal, patchy, and speckled.⁹² Near-infrared reflectance (NIR) is another imaging modality (as part of the SLO) used to evaluate retinal structure.³² The NIR-autofluorescence signal is thought to represent melanin.⁵⁹ Recently, the same team elucidated the benefit of a multimodal imaging assessment (FAF, NIR, SD-OCT) in β -thalassemic patients who were diagnosed with DFO-induced retinopathy. By modifying a classification system for pattern dystrophy, Viola et al, created the following categories: butterfly shaped-like, fundus flavimaculatus-like, fundus pulverulentus-like, vitelliform-like dystrophy, and minimal change.⁹¹ The results of these papers and others are summarized in Table 5.

5.2.1. Assessment of retinal function—The ERG is a functional evaluation of the retina. Synchronized activation of retinal cells leads to electrical currents released in the same direction, resulting in an electrical potential. The full field or global ERG is a mass electrical response of the retina to a light stimulus. In humans, corneal contact lens electrodes are employed to aid in recording the electrical potential that is emitted after a photic stimulation by the ERG light-emitting diodes (LEDs).⁷⁷ The photic stimulus elicits a

biphasic waveform composed of an a- and b- wave. The a-wave, the first large negative deflection, represents the photoreceptor potential from the outer retina. The b-wave, the first positive deflection, represents the ON bipolar cells and the Müller cell activation from the middle layer of the retina. Oscillatory potentials (OPs) are found on the ascending limb of the b-wave, and most likely represent a modulating effect of amacrine cells on the b-wave. Additionally, the c-wave originates in the RPE, and the d-wave indicates activity of the OFF bipolar cells. Furthermore, the electro-oculogram (EOG) is an eye-movement dependent voltage recorded between two electrodes placed at either corner (canthus) of an eye. The EOG measures the transepithelial potential (TEP) of the RPE. Recently, multifocal ERG (mfERG) has been developed to provide a detailed evaluation of the central retinal health. ⁷⁷

Several studies have employed ERG in their testing arsenal when evaluating DFO-induced retinopathy in β -thalassemic patients. Likely, retinal damage occurs through iron overload induced free radical damage or by way of DFO specific cellular toxicity. ^{10, 16} Jiang et al, demonstrated abnormal scotopic sensitivity thresholds, suggestive of rod dysfunction in patients who had received more than nine years of transfusion therapy without iron chelation. They concluded that iron might have damaged rods when the patients became iron overloaded. ⁵⁷ Moreover, they concluded that iron chelation therapy protected against iron induced retinal damage. ^{10, 16, 19, 57} Both Genead et al and Pan et al, presented case-reports of DFO-induced retinopathy and demonstrated no clinical alterations in ERG findings. ^{40, 71} Interestingly, Simons et al, demonstrated ERG and EOG alterations in a β -TM patient who was noncompliant with DFO chelation therapy. ERG demonstrated bilateral reduction in amplitude for photopic, scotopic, and 30 Hz flicker. Additionally, EOG measurements produced a diminished response. ⁸⁰ From the studies presented, ERG and EOG measures can provide additional information that can support DFO-induced retinopathy in β -TM patients. At the moment, it is unclear whether ERG and EOG provide early identification when compared to FAF, NIR, and SD-OCT.

6. Future directions

6.1. RPE Hemoglobin synthesis and secretion

Tezel et al demonstrated that RPE cells are capable of producing and secreting hemoglobin. ⁸⁸ The proposed necessity for RPE hemoglobin production is to maintain a steady flow of oxygen to the neurosensory retina. ^{58, 88} Interestingly, Tezel et al revealed hemoglobin is the most abundant protein in the normal human RPE. Furthermore, the RPE can be induced by monomethylfumarate to produce HbF *in vivo* and *in vitro*. ⁷³

There may be ineffective RPE hemoglobin expression in β -TM and β -TI patients. As mentioned, β -TM is caused by a quantitative loss of the beta gene and thus a decreased HbA tetramer production ($\alpha_2\beta_2$). This ineffective RPE hemoglobin production could lead to hypoxia induced retinal damage that contributes to the various thalassemia related retinal pathologies (Table 1).

6.2. Hepcidin regulation

β -thalassemics have low levels of hepcidin, an iron regulatory hormone. This permits more iron absorption from food. Recent studies in murine models have evaluated the role of the

serine protease TMPRSS6, which decreases hepcidin production. ^{78, 79} Another demonstrated that a combination of deferiprone (oral iron chelation therapy) and siRNA suppression of Tmprss6 provides a promising treatment for anemia and secondary iron loading seen in β -TI (transfusion independent thalassemia). ³⁵

Furthermore, this therapy may also be beneficial for β -TM (transfusion dependent thalassemia). Between blood transfusions, β -TM patients will have reactivated their endogenous erythropoiesis, leading to decreased hepcidin production causing increased intestinal iron absorption. ^{20, 35} Therefore, transfusion induced hemochromatosis can be controlled by using iron chelation therapy to reduce the stored iron from the body and potentially using a hepcidin analog (PR73, minihepcidin) to reduce the uptake of dietary iron. ^{20, 35, 69, 72, 78, 79}

7. Conclusion

Practitioners need to be vigilant to detect retinopathy caused by thalassemia itself, transfusional iron overload, or iron chelators. The availability of relatively new oral iron chelators now permits treatment that may minimize retinal complications. If retinal complications occur, close follow-up using various imaging modalities may help to lessen the retinal damage.

9. Method of Literature Search

In November, 2014, a comprehensive electronic search using the PubMed and Medline databases using the following single and combinations of key words (DFO retinopathy, ophthalmology, retinopathy, iron chelator induced retinopathy, hepcidin, beta-thalassemia intermedia, beta-thalassemia major, iron overload, retina, deferiprone, deferoxamine, angioid streaks, transfusional iron overload, and pseudoxanthoma elasticum-like) was used to collect pertinent publication in this field. Furthermore, references identified within these articles were also included. We collected and retrieved a total of 153 publications. From the 153 publications we included a total of 115 references. References were included if they discussed retinal abnormalities in beta-thalassemic major individuals. 101 references were cited in the main manuscript text and 14 unique references were cited in the “tables” section (tables section includes a total of 35 citations, 14 unique and 21 overlapping with manuscript text). Moreover, articles discussing deferoxamine induced retinal toxicity were included even without concurrent incorporation of beta-thalassemia major patients. We excluded references that did not demonstrate retinopathy that was caused by either transfusional iron overload or iron-chelator therapy toxicity. Discussions regarding future directions included references related to both beta-thalassemia major and intermedia pathologies when the article demonstrated content that was translational to both severities of disease. Two book chapters were included 1) because of analysis of iron chelators and discussion of iron induced retinal damage and 2) because of discussion of electrophysiology.

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TABLE 1
Meta-analysis for the prevalence of ocular abnormalities in β -Thalassemia patients

	β -TI/ β -TM combined		β -TI [^]		β -TM ⁺		Odds ratio for TI as compared to TM [^] (95% CI)	P-value
	n/N	Prevalence rate (95% CI)	n/N	Prevalence rate (95% CI)	n/N	Prevalence rate (95% CI)		
Lens Opacities	78/336	0.17 (0.03, 0.31)	3/35	0.05 (0.00, 0.11)	11/161	0.06 (0.00, 0.12)	2.00 (0.34, 11.7)	0.44
RPE abnormalities	120/336	0.34 (0.25, 0.43)	8/35	0.21 (0.01, 0.41)	48/161	0.29 (0.22, 0.36)	0.64 (0.23, 1.79)	0.39
Angioid streaks	5/336	0.01 (0.00, 0.02)	3/35	0.07 (0.00, 0.16)	2/161	0.01 (0.00, 0.03)	3.03 (0.35, 26.3)	0.32
RVT [§]	46/306	0.12 (0.05, 0.19)	7/30	0.19 (0.00, 0.37)	15/136	0.08 (0.02, 0.15)	2.63 (0.87, 7.96)	0.09

β -TM = β -Thalassemia Major; β -TI= β -Thalassemia Intermedia

[§] Does not include study by Rinaldi, as this feature was not evaluated in that study.

[^] Does not include studies by Anu Gaba or Sorcinelli.

⁺ Does not include study by Anu Gaba.

TABLE 2

Retinopathy due to transfusional iron overload

Author & Year	Study Type	Total Patient population	No DFO therapy	Average Age during study	Average # of blood transfusions	Average Ferritin (ng/ml)	Average serum iron (µg/dl)	Retinal findings
Taneja (2010) ³¹	Prospective observational	45	6	4.70	240	6300	602	RPE mottling, RVT, Disc hyperemia
Anu Gaba (1998) ²	Prospective, cross-sectional, case-control	140	32	10	--	3,394	184	RPE mottling
Aessopos (1992) ¹	Prospective observational, cross-sectional	100	21	26	483	4230	--	Angioid Streaks

TABLE 3

Iron chelators

Chelator	Advantages	Side effects	Disadvantages
Deferrioxamine	Extensively used clinically in the United States for transfusion induced iron overload	Retinopathy, ototoxicity, bone changes, pulmonary toxicity, growth failure, <i>Yersinia enterocolitica</i> infection	Expensive Only 5% of administered drug facilitates iron elimination Ineffective GI absorption, administration is either intravenous or subcutaneous
Deferiprone	Oral administration available Retinal iron chelation is noted	Agranulocytosis, arthropathy, neutropenia,	In low concentrations free radical formation may occur
Deferasirox	Oral administration available Single dosing per day due to extended half life Good absorption, effective chelator	Skin rash, nausea, abdominal pain, diarrhea	No documented retinal penetration

²⁴. Adapted from *The Role of Iron in Retinal Diseases*, in: "Studies on retinal and chorioidal disorders"

TABLE 4

Summary of DFO induced Retinopathy studies 1983-2014

Author (Year)	Study Type	Total # patients	Route	Cases of Retinopathy	Average Exposure to DFO (years)	Dosage of DFO (mg/kg/d)	Diagnostic Tests	Avg age (SD)	Nationality	Retinal findings	Relevant PMHx
Wu (2014) ³⁵	Case-report	1	SQ, IV	1	20	30 (SQ), acutely-98 (IV)	DPE, FP, NIR, SD-OCT,	34	Taiwanese	Multiple discrete hypo-pigmented circular lesions over posterior pole and mid-peripheral retina OU	--
Viola (2014) ³³	Retrospective chart review	20	SQ	20	32	--	DPE, FP, FAF, SD-OCT	45.1 (9.7)	Italian	DFO retinopathy- classified by specific fundus patterns: butterfly shaped, fundus flavimaculatus-like, fundus pulverulentus-like, and vitelliform-like changes. Deposition noted near Bruch membrane-RPE complex. RPE atrophy was noted in areas of pattern dystrophy-like changes.	--
Van Bol (2014) ³²	Case-report	2	IV	2	21 days	25 (patient 1 IV dose), 30 (patient 2 IV dose)	DPE, FP, FAF, FAF, SD-OCT	56.00	Belgian	Reversible serous detachment of neurosensory retina - associated with photoreceptor outer segment elongation - RPE mottling noted post-discontinuation	Both had AML- acute DFO exposure
Gelman (2014) ¹³	Case-report	1	--	1	--	--	DPE, FP, FAF, SD-OCT, ERG, EOG, micropertimetry	53.00	--	RPE mottling OU; infrared imaging showed increased areas of stippling through the macula OU; Fundus autofluorescence showed diffuse areas of stippled hyperautofluorescence and hypoautofluorescence OU; SD-OCT showed foveal disruption of the ellipsoid zone; attenuation of the photoreceptors; deposits within the RPE with central thickening of the RPE band OU; micropertimetry showed macular sensitivity depression and severe attenuation in the inferotemporal macular region OD; ERG showed delay in cone responses but showed normal rod responses	--
Viola (2012) ³⁴	Prospective, cross-sectional, case-control	197	SQ	18	32	Daily dose – 1 to 4.5 g	DPE, FP, FAF	41 (9.5)	Italian	4 phenotypic patterns – minimal change, focal, patchy, and speckled	--

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Author (Year)	Study Type	Total # patients	Route	Cases of Retinopathy	Average Exposure to DFO (years)	Dosage of DFO (mg/kg/d)	Diagnostic Tests	Avg age (SD)	Nationality	Retinal findings	Relevant PMHx
Simon (2012) ²⁹	Case-report	1	SQ, IV	1	--	40 (SQ dose), 50 (IV dose)	DPE, FP, FA, ERG, EOG	29.00	Cambodian	RPE mottling and blocked fluorescence in well-demarcated areas on FA	Patient presented with hepatic iron overload and was switched from SQ to IV DFO (50 mg/kg/d) acutely
Duval (2011) ¹²	Case-report	1	SQ, IV	1	40	--	DPE, FP, FA, TD-OCT	54	Caucasian	Vision loss due to choroidal neovascular membrane (CNVM); FA- diffuse RPE mottling and CNVM; 3x IV bevacizumab to treat CNVM	B-TI, hyper transfused and DFO therapy
Taneja (2010) ³¹	Prospective, observational	6	SQ	1	2	416g (entire dose)	DPE, FP, FA	11.30	Indian	RPE degeneration, retinal venous tortuosity	Average serum iron (mg/dl) = 250, average serum ferritin (ng/ml) = 2664, average # of blood transfusions = 23.4
Genead (2010) ¹⁴	Case-report	1	SQ	1	20	--	DPE, SD-OCT, ERG, FA, GKP, FAF, FP	45.00	Caucasian/Italian	Macular vitelliform lesion	Splenectomy, mild hearing impairment
Baath (2008) ⁵	Retrospective case series	84	IV, SQ	1	--	25-50	FA, ERG, EM	12.6 (5.6)	--	Mild pigmentary retinopathy, decreased central responses by ERG	--
Lu (2007) ²¹	Case-report	1	--	1	11	49-100	DPE, FP, ERG, GKP	36.00	--	Pigmentary retinopathy	--
Hidajati (2004) ¹⁷	Case-report	1	SQ, IV	1	--	6-24 (range of SQ dose), 63 (IV total dose)	VF, EOG, EM	61.00	Caucasian	RPE mottling OU	Splenectomy; DFO for autoimmune HA
Gonzales (2004) ¹⁵	Case series, non-consecutive	2	SQ (patient 1), IV (patient 2)	2	Patient 1-11mo, patient 2-3 years	Patient 1- 1g/2x daily/SQ; patient 2-2680mg/5x weekly for 3 years	DPE, FP, FA, FM, ERG, EOG, GMP	70.00	--	Patient 1- vitelliform macular lesions with hyperfluorescence on FA OU; macular pigment clumping and atrophic changes; ERG- reduction in cone-mediated responses; patient 2- vitelliform lesion with RPE mottling in macula OU; yellowish deposits with subfoveal pigmentary clumping without subretinal fluid	Both patients had myelodysplasia
Arora (2004) ⁴	Case-report	1	SQ	1	3	--	DPE, FP, FA, ERG, VEP	81.00	--	Symmetrical well-circumscribed area of abnormal pigmentation, maculae OU; FA- RPE atrophy without leakage; ERG- b-wave latency delay, subnormal cone predominant responses; VEP-OU delayed	Lymphoplasmacytic lymphoma; POAG
Bansal (2003) ⁶	Case-report	1	--	1	22	--	DPE, FP, FA	40.00	--	Subretinal macular pigment mottling OU; Bull's eye maculopathy OU	Peripheral neuropathy
Haimovici (2002) ¹⁶	Retrospective, observational case series	16	IV, SQ	16	3.18	2, 1.5, 3, 6	DPE, FA, ERG, EOG, FP	55.60	Caucasian, African-American	ERG and EOG helpful in confirming retinal and RPE dysfunction	Refractory anemia, chronic renal failure

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Author (Year)	Study Type	Total # patients	Route	Cases of Retinopathy	Average Exposure to DFO (years)	Dosage of DFO (mg/kg/d)	Diagnostic Tests	Avg age (SD)	Nationality	Retinal findings	Relevant PMHx
Jiang (1998) ¹⁸	Prospective, cross-sectional, case-control	11	SQ, IV	3	12.1	20-50	DFE, ERG	17.00	--	3 patients had altered retinal function, not specifically retinopathy	--
Anu Gaba (1998) ²	Prospective, cross-sectional, case-control	140	SQ	8	2.7	3.93g/mo.	DFE, FA, FP	10.00	Indian	RPE mottling	--
Spraul (1996) ³⁰	Case-report	1	--	1	4mo.	1g/d; 6g /week	DFE, ERG, GMP, FM	8.00	German	Bilateral tortuous vessels, RPE mottling and atrophy.	Aplastic anemia-transfusional iron overload
Dennerlein (1995) ¹¹	Prospective, cross-sectional, case-control	17	--	6	--	40-120	DFE, ERG, GKP, EOG, FP, VEP	5 to 25 (range)	German	RPE changes, retina vessel tortuosity	--
Melita (1994) ²³	Case-report	1	SQ	1	13 mo.	1g SQ 2x/d	DFE, FP, FA, FM, ERG, GMP	70.00	--	Fine, granular RPE changes in maculae OU; FA mottled hyperfluorescence with punctate areas of blocked fluorescence OU	5q-minus myelodysplasia, refractory anemia
Marciani (1991) ²²	Case-series	10	SQ, IV	4	--	50	VEP	19.90	Italian	VEP abnormalities included delayed P100 latency in the absence of visual disturbances OU	--
Ravelli (1990) ²⁸	Case series	15	IV	13	--	40	DFE, VEP, EOG, FA	61 (10)	--	Decreased VA or color vision dysfunction; 4 developed maculopathy; 5-electrooculogram abnormalities; 5-fluorescein angiographic findings of RPE pathology	DFO given to patients for aluminum overload
Cases (1990) ⁸	Prospective	41	IV	7	--	10-40 mg/kg/3xweek	DFE, FM	63.00	--	Color vision abnormalities; one patient developed perimacular pigmentary deposits	Hemodialysis patients
Pull (1989) ²⁶	Case series	3	IM	3	--	14 daily doses of 1g	EOG, ERG, VEP	62.70	--	RPE atrophy and mottled hyperfluorescence	Patients had rheumatoid disease
Kaplinsky (1988) ¹⁹	Case-report	1	IV	1	--	130-180 (IV)/daily	ERG, VEG	4.00	--	Bilateral optic neuropathy, noted by ERG and VEP. No further clarification provided.	Juvenile chronic myeloid leukemia
De Virgillis (1988) ¹⁰	Prospective, observational	15	SQ, IV	9	10 months	40-60 (SQ); 10-12g (IV)	DFE, GKP, ERG	9 to 16 (range)	--	High doses of IV DFO produced reversible minor retinal toxicity; 3-permanent, 6- transient	--
Rahi (1986) ²⁷	Case-report	1	IM, IV	1	16	500mg /daily; acute-IV- 165	ERG, DFO	24.00	--	Light and electron microscopic changes to the RPE associated with DFO—patchy depigmentation, swelling, calcification of mitochondria, disorganization of plasma membrane, loss of microvilli from apical surface, and vacuolization of the cytoplasm	Splenectomy

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Orton (1985) ²⁵	Case-report	2	SQ	0	3mo.	2g/day	DFE, VER, ERG, GMP, FA	4.25	Jordanian	No evidence of pigmentary retinopathy. Bilateral disc edema present, FA: late leakage of dye in inferior and superior poles of each optic nerve. ERG: abnormal scopic and photopic findings. VER: abnormal wave forms	
Blake (1985) ⁷	Case-series	7	IV	3	--	Patient 1: 3g/d for 5d	DFE, PF, ERG, EOG	57.00	--	Pt3 – OD- arcuate field defect with right optic atrophy – ischemic optic neuropathy	--
						Patient 4: 15g/over 5 d				Pt4- fine pigmentary stippling of maculae OU	
						Patient 7: 3g/12d				Pt7- (12 days of DFO exposure) bilateral pigmentary retinopathy	
Lakhanpal (1984) ²⁰	Case-series	8	IV	7	6.4 days	4.9g/d	DFE, FA, ERG, EOG, VEP	69.40	--	First to describe Pigmentary Retinal degeneration, developed in 7 out of 8 patients	--
Arden (1984) ³	Prospective, cross-sectional, case-control	43	SQ	--	--	--	DFE, FP, FA, GMP, EOG, ERG	18.00	Greek, Turkish, Indian	Dark adaptation- four patients had abnormal rod thresholds; Fundus-RPE hyperpigmentation	--
Davies (1983) ⁹	Case-series; non-consecutive	4	IM, SQ, IV	2	--	Patient 1: 500mg/d (IM), 2.5g/ wk. (SQ), 75- 235mg/kg/d for 86d (IV)	DFE, FA, ERG, EOG, VEP	22.00	--	2 out of 4 patients developed transient retinal abnormalities. One patient developed retinal stippling OU. Another patient with 11 years of IM DFO developed thinning and tortuosity of retinal vessels	Splenectomy
						Patient 4: 500mg/d (IM), 165mg/kg/ for 2d, 220mg/kg/d for 6 days					

DFO- Deferrioxamine; SQ- subcutaneous; IV- intravenous; TD-OCT- Time domain optical coherence tomography; SD-OCT-Spectral-domain optical coherence tomography; OU-both eyes; OD-right eye; OS- left eye; AML- acute myelocytic leukemia; DFE-dilated fundus exam; FP-Fundus photo; FA- fluorescence angiography, FAF-fundus autofluorescence; SLO- confocal scanning laser ophthalmoscopy; NIR- near-infrared reflectance imaging; ERG- electro-retinogram; EOG-electro-oculogram; GMP- Goldmann kinetic perimetry; HA- autoimmune hemolytic anemia; FM- Farnsworth-Munsell 100-hue test; VEP- visual evoked potentials; IM- intramuscular; PMHx- past medical history; POAG-primary open angle glaucoma.

TABLE 5

Disease Management with Multimodal imaging

Author (Y ear) (# Patients affected/Total)	Fundus photography	FAF	NIR	SD-OCT
Wu (2014) ³⁵ (1)	Multiple discrete hypo-pigmented rounded lesions over the posterior pole and mid-peripheral retina OU	--	(Fig. 2) Hyper-reflective deposits, para- and peri-foveal areas	(Fig. 3) ■ Multiple confluent hyper-reflective deposits in Chr, RPE, and IS/OS junction ■ Thickened RPE, Bruch's membrane + Chr ■ IS/OS junction severely disrupted at peri- and para-foveal areas
Wu et al 2014 DFO History and Chelator change: ■ B-TM; 30mg/kg/d for 20yrs (SQ); 98mg/kg for 42d (IV) ■ DFO to Deferasirox/deferiprone Follow-up findings: ■ Note- the patient NIR and SD-OCT images were taken 6 weeks after he discontinued DFO and switched to a Deferasirox/DFO regimen				
Viola (2014) ³³ (20/290)	Butterfly shaped-like (Fig. 1A, 2A-F) Radiating yellow pigment lines, with brown hyper-pigmented granular and focal material	Butterfly shaped-like (Fig. 1C, 2A-F) ■ Yellow and brown pigmented material corresponded to increased FAF signal ■ Mild hyper- or hypo- autofluorescent areas in macula	Butterfly shaped-like (Fig. 1B, 2A-F) Yellow and brown pigmented material corresponded to increased NIR signal	Butterfly shaped-like (Fig. 1F-G, 2D-F) ■ Yellow and brown areas corresponded to thick + highly reflective dome-shaped lesions ■ These lesions disrupted outer layers in foveal or perifoveal regions ■ Hyper and hypo-fluorescent areas corresponded to thickening of IS/OS junction and RPE thinning.
	Fundus flavimaculatus-like (Fig. 3A-C) Yellowish subretinal flecks	Fundus flavimaculatus-like (Fig. 3A-C) Hyper-autofluorescent areas	Fundus flavimaculatus-like (Fig. 3A-C) Flecks were barely visible	Fundus flavimaculatus-like (Fig. 3A-C) Granular hyper-reflective subretinal deposits reaching into OPL and interrupting the ELM
	Fundus-pulverulentus-like (Fig. 4) RPE mottling, coarse punctate, at the posterior poles and near arcades	Fundus-pulverulentus-like (Fig. 4) RPE mottling- appeared as hyper-autofluorescent dots	Fundus-pulverulentus-like (Fig. 4) RPE mottling appeared as hyper-reflective dots	Fundus-pulverulentus-like (Fig. 4) Subretinal granular hyper-reflective deposits; ELM is partially interrupted
	Vitelliform-like (Fig. 5A-E) Rounded yellowish sub-macular lesions OU	Vitelliform-like (Fig. 5A-E) Intensely hyper-autofluorescent	Vitelliform-like (Fig. 5A-E) Hypo-reflective	Vitelliform-like (Fig. 5B-E) ■ Yellowish lesions localized to homogeneous hyper-reflective material in the subretinal space above RPE ■ Associated diffusely thickened IS/OS junction but intact ELM
	Minimal macular change	Minimal macular change	Minimal macular change	Minimal macular change

Author (Y ear) (# Patients affected/Total)	Fundus photography	FAF	NIR	SD-OCT
	1 or 2 rounded small yellow-grey lesions 1 or 2 rounded small yellow-grey lesions	(Fig. 5) Lesions corresponded to hyper-autofluorescent dots	(Fig. 5) Lesions corresponded to hyper-reflective dots	(Fig. 5) Lesions corresponded to focal thickening or bumps of the RPE-basal lamina drusen
<p>Viola et al 2014 DFO History and Chelator change: ■ Beta-thalassemia (major or intermedia unspecified); 1.5-4.5 g/d (SQ) for an average of 32.7 ± 8.7yrs ■ 6 patients switched to deferasirox; 13 patients remained unchanged; 1 patient discontinued DFO Follow-up findings: Butterfly shaped-like ■ Average follow-up time = 19.7 ± 8.8 mo (range= 10-45mo) ■ Progressive enlargement of RPE atrophy in affected hyper-autofluorescent foveal areas. ■ RPE atrophy associated with outer retinal layer atrophy and tubulation over the RPE atrophy Fundus flavimaculatus-like ■ Progressive fading of perifoveal granular hyper-autofluorescent flecks ■ Progressive RPE atrophy; SD-OCT interruption of outer retinal layers and RPE atrophy, marked thinning of ONL Fundus pulverulentus-like ■ Subretinal granular hyper-reflective deposits increased in # and size, spared the fovea, and became more widespread and confluent around the fovea ■ No major RPE atrophy in foveal area Vitelliform-like ■ Gradual increase in yellowish material in terms of size and hyper-autofluorescence ■ Resolution of vitelliform material beneath fovea; RPE atrophy exposed ■ Several subretinal deposits gradually developed around macula + network of rounded irregularities- corresponding to decreased FAF and NIR signals + resembled reticular drusen ■ SD-OCT- showed macular IS/OS junction loss with underlying RPE atrophy, absent ELM, thinning of ONL Minimal macular change ■ Moderate enlargement and increased # of lesions on FAF and NIR imaging ■ None of the patients developed into pattern-like dystrophy</p>				
Van Bol (2014) ³² (2/2)	Patient 1: macular transparency loss; 5d post initial symptoms- RPE mottling	(Fig. 3) Patient 1: decreased autofluorescence; 5d post initial symptoms RPE mottling corresponded to clumped hyper- and hypo-autofluorescence zones – more in OS.	--	(Fig. 1) Patient 1: mild serous detachment of NR OU; macular layer photoreceptor outer segment layer elongation.
	Patient 2: cotton-wool spots around the vascular arcades + impaired macular reflection	(Fig. 6) Patient 2: reduced autofluorescence	--	(Fig. 4) Patient 2: bilateral serous detachment of NR, elongation of photoreceptor outer segments.
<p>Van Bol et al 2014 DFO History and Chelator change: ■ Patient 1: 52 F p/w AML; IV DFO 30mg/kg/d for 21d; increased to 48 mg/kg/d during last 8ds. ○ DFO stopped at diagnosis of DFO induced retinopathy ■ Patient 2: 60 F p/w AML; IV DFO 25mg/kg/d for 20d; increased to 30mg/kg/d during last 8ds. ○ Discontinued DFO due to worry that cotton-wool spots were caused by DFO toxicity Follow-up findings: ■ Patient 1: SD-OCT RPE regularities and reduced outer segment elongation ■ Patient 2: SD-OCT disappearance of serous detachment; RPE was fragmented, irregular and thickened; OU RPE mottling- corresponding to FAF hyper-autofluorescent foci + hyper reflective RPE irregularities on SD-OCT</p>				
Gelman (2014) ¹³ (1)	(Fig. 1) Mottling and pigmentary changes OU	(Fig. 2A-B, 3A-B) Diffuse areas of stippled hyper- and hypo-autofluorescence OU; plaque of central hyper-autofluorescence (similar to vitelliform	(Fig. 2C-D) Foci of increased stippling through macula OU	(Fig. 4) ■ Foveal disruption of ellipsoid zone, attenuated photoreceptors, and

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Author (Y ear) (# Patients affected/Total)	Fundus photography	FAF	NIR	SD-OCT
	pigmentary lesion with mild RPE mottling and clumping pigmentary lesion with mild RPE mottling and clumping			
Genead et al 2010 DFO History and Chelator change: ■ 45 White/Italian F w/ B-TM and chronic IM and SQ DFO therapy for 20yrs Follow-up findings: N/A				

DFO- Deferrioxamine; DFP- deferiprone; SQ- subcutaneous; IV- intravenous; SD-OCT-Spectral-domain optical coherence tomography; OU-both eyes; OD-right eye; OS- left eye; AML- acute myelocytic leukemia; DFE-dilated fundus exam; FP-Fundus photo; FAF-fundus autofluorescence; SLO- confocal scanning laser ophthalmoscopy; NIR- near-infrared reflectance imaging; IM- intramuscular; Chr- choroid