Incidence of Ocular Toxicity from Iron Chelating Agents at Siriraj Hospital

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ABSTRACT

Objective: To determine the incidences of ocular toxicity and ocular findings, including structural and functional abnormalities, caused by iron chelating agents and detected by an electrophysiologic test at Siriraj Hospital.

Methods: A retrospective chart review was conducted of patients receiving multiple blood transfusions and iron chelation therapy who had an eye examination at Siriraj Hospital between January 1995 and December 2017.

Results: Ninety-seven charts were reviewed. The 88 patients included comprised 41 males and 47 females. Their ages ranged from 1 year 11 months to 47 years, with children predominant (mean: 8.13 years). Beta thalassemia HbE was the main diagnosis (87.5%). After receiving iron chelating agents, 3 patients had abnormal eye findings with suspected ocular toxicity. Two had retinal pigmentary changes, but only one of those two displayed a mildly decreased response in a scotopic electroretinogram. Although the third patient also showed a decreased electroretinogram response, there were no obvious retinal changes. All three received the iron chelating agents desferrioxamine, deferiprone, and/or deferasirox at different doses and for various durations.

Conclusion: Although some pigmentary retinopathy and decreased electroretinogram responses were found, leading to ocular toxicity being suspected, there was a very low incidence of ocular toxicity from the chelating agents. In addition, the dosages of the agents causing ocular toxicity, and the duration of that toxicity, were inconclusive. Moreover, a gold standard for identifying ocular toxicity caused by chelating agents was not able to be established. Consequently, the risks and benefits of employing eye screening coupled with an invasive procedure like an electrophysiologic test will need to be weighed, especially with pediatric patients.

Keywords: Ocular toxicity; iron chelating agent; thalassemia; electroretinogram (Siriraj Med J 2020; 72: 209-213)

INTRODUCTION

Thalassemia, an inherited blood disorder, has a high incidence rate in Thailand. Its treatment depends on the type and severity of the disease involved. Although blood transfusions are a treatment option for patients with anemia, an iron overload can occur following multiple blood transfusions, which can be potentially fatal. Chelation therapy utilizing iron chelating agents helps to remove the excessive iron from the body.

The iron chelating agents used at Siriraj Hospital are desferrioxamine, deferiprone, and deferasirox. Unfortunately, their use may lead to ocular toxicity, presenting in the form of a deterioration in visual acuity and color vision, night blindness, a scotoma or constricted visual field, retinopathy, optic neuropathy, and an abnormal retinal function detectable by electroretinogram (ERG).[1-5] Little information has been reported on the incidences of these ocular toxicities, and there are no standard eye-screening guidelines for patients.

Our study aimed to determine the incidences of ocular toxicity and ocular findings, including both structural and functional abnormalities, detected by ERG and

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arising from the use of iron chelating agents at Siriraj Hospital.

MATERIALS AND METHODS

A retrospective chart review was conducted of patients who received multiple blood transfusions with iron chelation therapy and had an eye examination at Siriraj Hospital between January 1995 and December 2017. Excluded from the study were patients who had abnormal eye conditions before receiving iron chelating agents, such as a previous optic neuropathy or retinopathy due to toxic agents or other causes. This study was conducted after approval by the Siriraj Institutional Review Board, Faculty of Medicine Siriraj Hospital, Mahidol University (Si 233/2017).

The baseline visit was defined in two ways. If a patient had not yet been administered any chelating agents, it was deemed to be that visit when the patient had a normal eye examination. However, in cases where a patient had already commenced the use of the agents, the baseline visit was the first visit after the treatment had begun when a normal eye examination was performed. Demographic data (age, sex, body weight, and height) were recorded. The diagnosis, type and dosage of each iron chelating agent received, and serum ferritin level were also recorded. The eye examinations included LogMAR visual acuity measurements, anterior segment and fundus examinations, color vision tests, visual field tests, and electrophysiologic tests. The follow up eye examination is routinely done yearly.

Ocular toxicity from the agents was defined as either a decrease in the best corrected visual acuity (expressed in a LogMAR scale) of more than two steps from a patient's baseline, or any abnormal finding in any part of an eye examination.

Statistical analysis

A descriptive statistical analysis of the quantitative data was performed by determining the mean, minimum, and maximum values. All analyses were carried out using SPSS Statistics for Windows, version 18 (SPSS Inc., Chicago, IL, USA).

RESULTS

A 97-chart review was conducted. The 88 included patients comprised 41 males and 47 females. Their ages ranged from 1 year 11 months to 47 years. However, with a mean of 8.13 years, most patients were children. Beta thalassemia HbE was by far the most common diagnosis (87.5%).

After receiving iron chelating agents, 3 patients were found to have abnormal eye findings suggestive of ocular toxicity (Table 1).

Patient one:

This was a 9-year-old girl with beta thalassemia HbE. She received deferasirox (21 mg/kg/day) for about 12 months before switching to deferiprone (31.9 mg/kg/day initially, but adjusted to 60 mg/kg/day) for around 17 months. Desferrioxamine (16 mg/kg/day) was subsequently added.

At the toxic visit, she was 17 years old. By that stage, she had received the agents for 7 years. Her serum ferritin level was 4,148 ng/ml. Changes in the pigment of the retina were found in both eyes, but her visual acuity, color vision, and visual field were unremarkable. An ERG was not performed during that visit.

Patient two:

This was a 6-year-old boy with beta thalassemia HbE. He received desferrioxamine (20 mg/kg/day) for about 3 months before the dose was increased to 40 mg/kg/day and deferasirox (35 mg/kg/day) was added. He received both agents for approximately 48 months, and then they were stopped. Following a 3-month cessation, the chelation therapy was recommenced using deferasirox (31 mg/kg/day). After 8 months, the agent was switched to deferiprone (71 mg/kg/day) and desferrioxamine (no dosage was recorded).

At the toxic visit, he was 15 years old. His serum ferritin level was 1,912 ng/ml. A pigmentary change was found in the retina of both eyes, and he had a mildly decreased scotopic ERG for both eyes. Other ocular findings were unremarkable.

Patient three:

This was a 6-year-old girl with beta thalassemia HbE. She initially received desferrioxamine (no dosage was recorded). Four years later, deferiprone (80 mg/kg/day) was added. Because she developed liver toxicity, the chelating agents were given off and on.

At the toxic visit, she was 20 years old. She received deferiprone (89.5 mg/kg/day). Her serum ferritin level was 894.3 ng/ml. Only an abnormal photopic and scotopic ERG were found. Otherwise, her ocular findings were normal.

DISCUSSION

Iron chelating agents are used for the treatment of iron overload in patients with hematologic conditions that require frequent blood transfusions to prevent hemosiderosis. If left untreated, hemosiderosis may lead

TABLE 1. Three cases were suspected to have ocular toxicity from the iron chelating agents.

Patient (no.)	Age at 1st visit (year)	Age at toxic visit (year)	Iron chelating agents at toxic visit	Dose of each agent (mg/kg/day)	Serum ferritin at toxic visit (ng/ml)	Abnormal eye findings
1	9	17	Deferiprone Desferrioxamine	60 16	4,148	Pigmentary changes at retina in both eyes
2	6	15	Deferiprone Desferrioxamine	71–85 Not recorded	1,912	Pigmentary changes at retina in both eyes Mildly decreased scotopic ERG in both eyes
3	6	20	Desferrioxamine Deferiprone	Not recorded 89.5	894.3	Decreased ERG response in both eyes

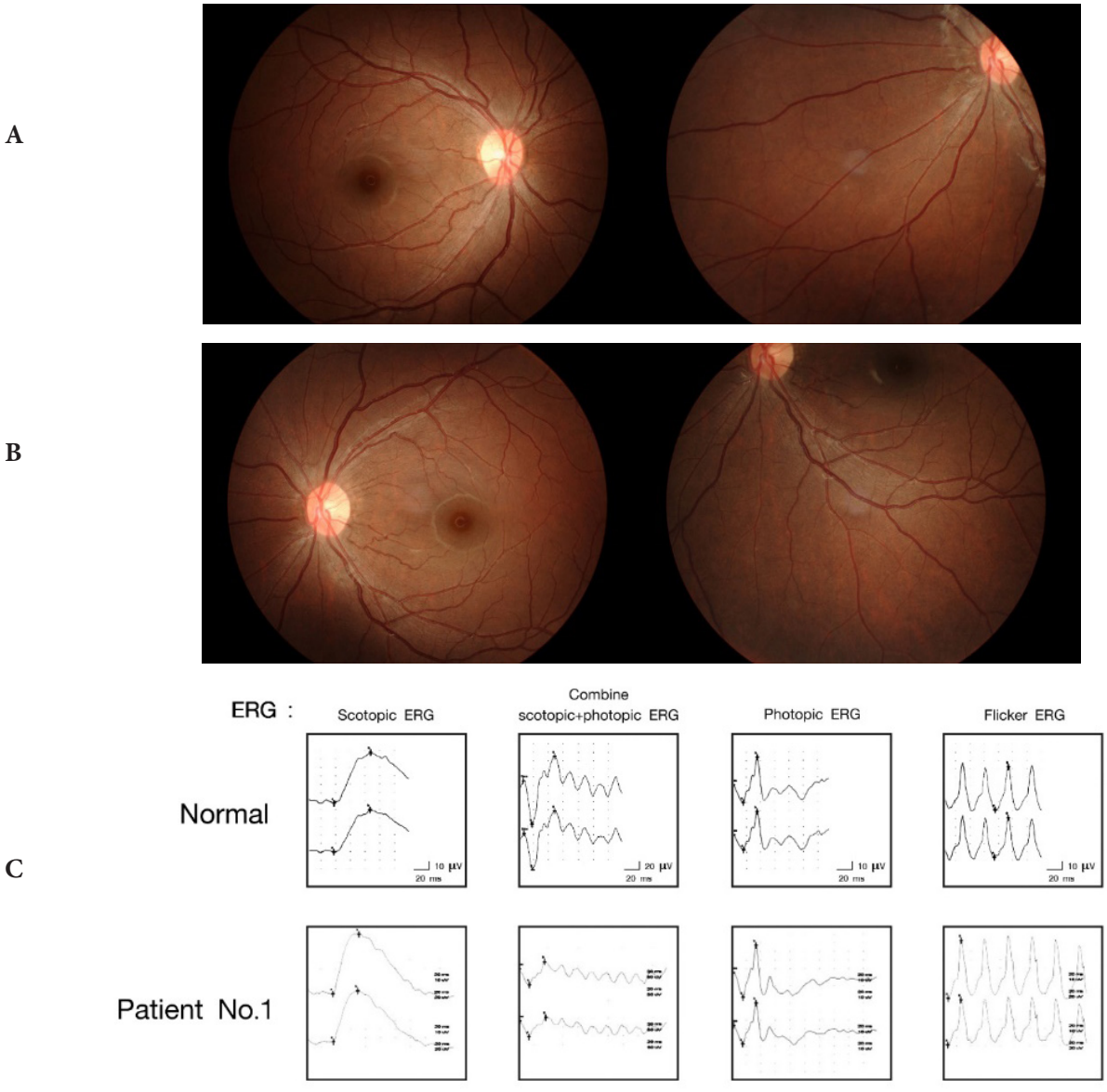

Fig 1. Fundus photography of the patient No.1 showed pigmentary retinopathy of the right eye **(A)** and left eye **(B)**. Normal ERG findings in both eyes (**C**: upper=right eye, lower=left eye).

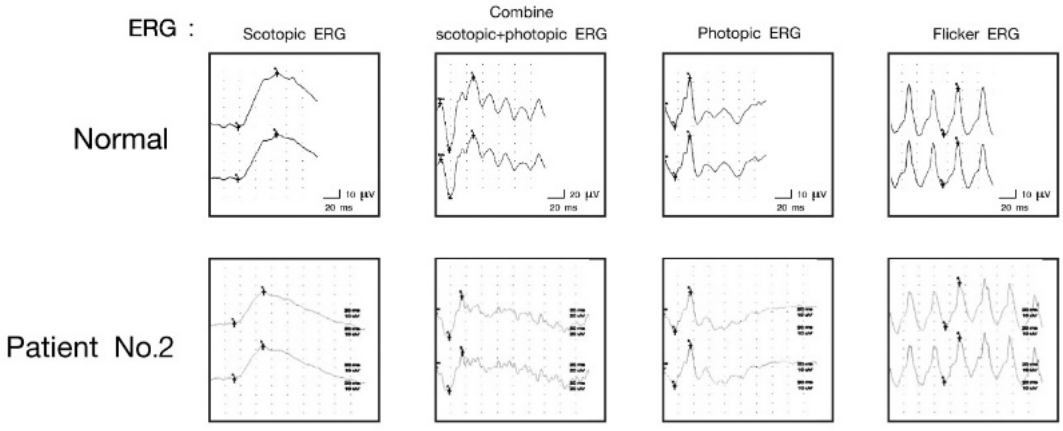

Fig 2. ERG findings in patient No.2 showed mildly decreased scotopic ERG in both eyes (upper=right eye, lower=left eye).

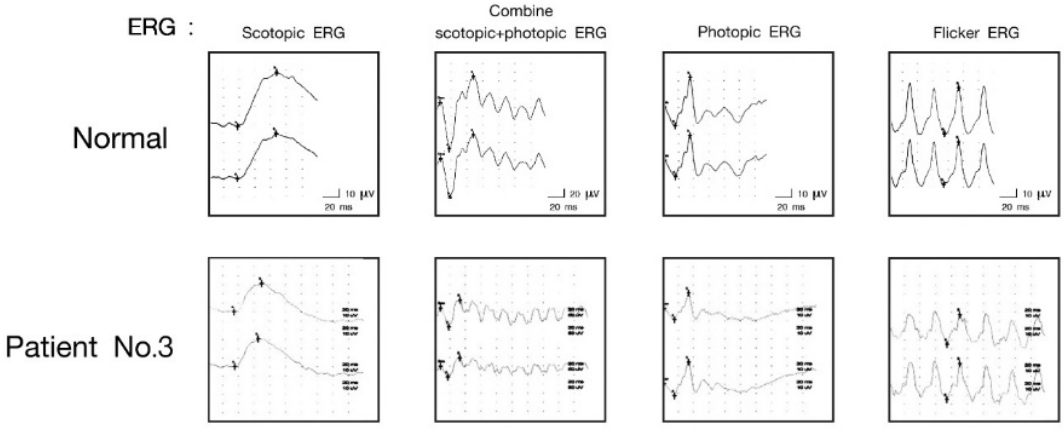

Fig 3. ERG findings in patient No.3 showed decreased photopic and scotopic ERG in both eyes (upper=right eye, lower=left eye).

to diabetes, cardiac disease, and hepatic dysfunction. There are many administration routes (for example, oral, subcutaneous and intravenous).

Desferrioxamine is widely used as an iron chelating agent for both intravenous and subcutaneous administration. It has a systemic toxicity effect on the cardiovascular, respiratory, gastrointestinal, cutaneous, and nervous systems. Bone dysplasia and high-frequency sensory neuronal hearing loss have been reported[1]. As to ocular toxicity, desferrioxamine can cause nyctalopia, abnormal color perception, visual field defects, cataract formation, optic neuropathy, and pigmentary retinopathy.[5] Various mechanisms of desferrioxamine toxicity have been hypothesized, such as the induction of oxidation that damages the blood-retinal barrier and reduces the concentration of other metal ions, like Cu^{2+} and Zn^{2+}.[6] It is still unclear whether ocular toxicity is dose-dependent or not. However, Simon S et al.,[7] showed that the risk of developing systemic toxicity increased with lower iron loads and with desferrioxamine dosages higher than 50 mg/kg/day.

Deferiprone, an alternative or adjunctive regimen to desferrioxamine, is orally administered. It is able to cross the blood-retinal barrier, and it has been reported to cause damage to the retinal pigment epithelium (RPE).[8]

Deferasirox is a newer, oral-efficient, iron chelator. There has been a case report of deferasirox inducing maculopathy, which was demonstrated by optical coherence tomography.[9]

A study by Baath JS et al.,[10] reported that desferrioxamine-related ocular toxicity was a rare and mild finding. Out of 84 patients who received regular desferrioxamine treatment, only one (1.2%) had desferrioxamine-related ocular toxicity. The researchers found central blurriness and retinal pigmentary changes, shown by examination and decreased central responses in electroretinography. Nevertheless, those changes proved to be completely reversible after a change from intravenous to subcutaneous therapy at a reduced dose. Maura Di Nicola et al.,[1] reported desferrioxamine-related, sight-threatening, ocular toxicity involving the RPE. Damage to the RPE can lead to visual field defects, color vision defects, abnormal electrophysiological

tests, and permanent visual deterioration. Haimovici et al.,[5] described early and unusual features in 16 patients with desferrioxamine-induced retinal toxicity. They found macular and/or peripheral pigmentary changes, reduced electroretinographic amplitudes, and reduced electrooculographic light-peak to dark-tough ratios. Peripapillary, papillomacular, and paramacular patterns of retinal pigment epithelial degeneration were also observed in one patient. Cohen et al.,[11] studied 52 regularly transfused patients who received desferrioxamine by subcutaneous or intravenous infusion. A symptomatic loss of vision and hearing developed in one patient. Both problems improved when chelation therapy was ceased.

In our study, we found 3 patients who were suspected to have ocular toxicity resulting from iron chelating agents. Two had pigment alterations in their retinas, but only one of those two had a mildly decreased response in a scotopic ERG. Although the third patient had a decreased ERG response, there were no obvious retinal changes. All 3 patients had no ocular symptoms or any disturbance in their visual acuity, color vision, or visual field. They all received desferrioxamine, deferiprone, and deferasirox as iron chelating agents at different doses and for a variety of durations.

In conclusion, there is a very low incidence of ocular toxicity arising from the use of these iron chelating agents. Our 22-year chart review revealed only 3 patients who were suspected to have ocular toxicity from objective testing, but without any apparent ocular symptoms. The dosages of these agents that caused the ocular toxicity, and the duration of that toxicity, were still inconclusive, as indicated by our findings and the previous studies mentioned above. No gold standard for identifying the ocular toxicity arising from these agents was able to be established. Consequently, eye screening with an invasive procedure, such as an electrophysiologic test, should be considered after assessing the related risks and benefits, especially with pediatric patients.

We could not calculate the incidence of this toxicity due to a small number of sample size. Our study was a retrospective study and had some limitations. First, there was a lack of detail in the patients' charts about the dosages of the iron chelating agents given. In addition, several agents were frequently given at the same time, which means that the ocular toxicity could have resulted from either any one of them or the particular combination of agents. Second, each patient could not complete all investigations such as lacking of visual field test in young patient. Finally, although the incidence of thalassemia in Thailand is high, eye examinations are not routinely provided; this means that cases of ocular toxicity may go undiagnosed.

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