Vision Impairment After Iron Chelating Agent in a Patient Under Peritoneal Dialysis

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INTRODUCTION
Vision disorders are a common problem in end-stage renal disease (ESRD) patients. Most patients under regular dialysis have diabetes mellitus and hypertension. In these subjects, vision problems are commonly related to diabetic retinopathy and hypertensive retinopathy.

On the contrary, drug side effects are uncommon causes of vision disorders.

In the past, aluminum (Al) overdose or toxicity was also considered common in ESRD patients. Chelating agents have been successfully used to treat Al-related disorders. Among their side effects, there are mild local reactions at the injection site, anaphylactic reactions, cataracts, ocular toxicity, and neurotoxicity.

CASE PRESENTATION
A 54-year-old female patient had a history of ESRD under regular continuous automatic peritoneal dialysis (CAPD) therapy for 6 years. She had underlying hypertension history under oral hypertensives (olmesartan medoxomil). She was admitted to the ward for iron chelating agent therapy due to high ferritin level (5480 ng/ml). Deferoxamine 1 gram was prescribed with intravenous drip for 24 hours for 5 days. On the fifth day, she complained about vision problems, i.e. central halo pattern vision loss. A deferoxamine-related macula edema was diagnosed. After discontinuing the medication, her vision gradually improved. After 3 months of follow up, her vision disorders recovered.

Although we reduced the dose of iron chelating agent, vision side effects also occurred in this ESRD patient.

This case taught us to perform a careful detection of vision problems before, during, and after deferoxamine therapy in order to prevent irreversible vision disorders.

Keywords: Vision Disorders; Kidney Failure, Chronic; Peritoneal Dialysis; Deferoxamine

Abstract
A 54-year-old female patient had a history of end-stage renal disease (ESRD) under continuous automatic peritoneal dialysis (CAPD) therapy for 6 years. She had underlying hypertension history under oral hypertensives (olmesartan medoxomil). She was admitted to the ward for iron chelating agent therapy due to high ferritin level (5480 ng/ml). Deferoxamine 1 gram was prescribed with intravenous drip for 24 hours for 5 days. On the fifth day, she complained about vision problems, i.e. central halo pattern vision loss. A deferoxamine-related macula edema was diagnosed. After discontinuing the medication, her vision gradually improved. After 3 months of follow up, her vision disorders recovered.

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led to chronic kidney failure. She was taking folic acid 5 mg 1 tablet every alternate day (QOD), olmesartan medoxomil 20 mg 1 tablet daily, and calcium acetate 1 tablet thrice with meal. Previously, she was given oral iron support 100 mg per day for 3 years due to chronic anemia and ESRD status. Blood transfusion was given 2 units per every 3 months for 3 years. Serum iron level and transferrin levels were monitored every 3 months, according to the guidelines from Kidney Disease Improving Global Outcomes (KDIGO) [1]. She wasn’t given iron tablets due to high iron level in the last 3 years. Blood transfusion was reduced to prevent further iron overload. We maintained hemoglobin level (Hb) around 8 g/dl. In the outpatient department, high ferritin level (5480 ng/ml on 27 Feb 2018) was noted. She also had complained about non-specific symptoms, like weakness and malaise. Therefore, she was hospitalized for iron overload therapy on March 2018. Table 1 reports laboratory data.

For iron overload study, hepatic iron concentration was not measured because not available in our hospital. Deferoxamine test was not performed because aluminum toxicity was rare in the current dialysis setting and with frequent blood transfusion therapy.

Her vital signs were as follows: body temperature 36.6°C, pulse rate 76/min, blood pressure 136/89 mmHg. General examination was unremarkable except peritoneal dialysis (PD) catheter at the left lower quadrant of the abdomen. Neither diffuse abdominal pain, nor abnormal mass were detected. Her vision fields were all normal because she could do PD exchange by herself.

We also consulted a hematologist for dosage of iron chelating therapy, who suggested to use deferoxamine 1-gram intravenous drip for 24 hours for 5 days.

She didn’t have any discomfort during the first 3 days of therapy. On the fifth day, she complained about vision problems, which she noted during PD exchange. She had already complained about the halo vision impairment on the fourth day, and color blindness was noted. Her visual field defect progressed. An ophthalmologist was consulted for the vision problems. After examination, macula edema was impressed, and it was suggested to stop deferoxamine therapy. The ophthalmologist suspected that the visual problem was related to deferoxamine injection. Fundoscopy and optical coherence tomography (OCT) confirmed macula edema (Figures 1 and 2).

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We immediately discontinued intravenous drip therapy and performed frequent assessment of her vision condition during hospitalization. Her vision condition improved before discharge, when she could again exchange her PD dialysate fluid by herself. Follow-up visits were arranged by ophthalmologist. OCT was done one month after discharge, then 5 months after discharge. The macula edema of both eyes recovered, and vision condition improved.

**DISCUSSION**

There is a myriad of diseases that affect both the eyes and kidneys (oculorenal syndromes) [2]. In our clinical practice, half of dialysis patients have underlying diabetes mellitus, mainly accompanied by diabetes retinopathy and glaucoma [3]. Hypertensive retinopathy may also result in vision disorders. Vision problems in dialysis may also be due to the retinal vessel’s stenosis or occlusion. In addition, the side effects of medications should be considered as one of the causes of vision disorders.

Among the ocular problems in chronic kidney disease and hemodialysis there are:
- glaucoma;
- metastasis calcification of cornea and conjunctiva;
- band keratopathy;
- superior limbic keratoconjunctivitis;
- cataracts;
- retinal detachment;
- macular leakage;
- retinal hemorrhage;
- drug toxicity; and
- optic neuropathy (anterior ischemic neuropathy or uremic optic neuropathy) [3].

Malignant hypertension can result in acute, substantial loss of vision owing to ischemic optic neuropathy and severe maculopathy. This condition may be checked through fundus examination [4], and an aggressive control of blood pressure results in a gradually recover of retinopathy.

Diabetic retinopathy is present in almost all type 1 diabetes patients with nephropa-
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Deferoxamine (DFO) is one of the medications used to treat aluminum intoxication, even though in the current practice it is not very frequent, while iron overload is more common. DFO chelates aluminum in dialysis patients, and iron in dialysis or hemosiderosis patients. It has high affinity for ferric iron, thus removing iron from hemosiderin, ferritin, and transferrin.

In peritoneal dialysis patients, DFO can be given by intravenously or intraperitoneal route, resulting in similar iron clearance degrees. Iron-deferoxamine complex is a water-soluble middle molecule range, thus it can clear more efficiently during peritoneal dialysis. It may have several side effects: hypotension, anaphylaxis, and hearing disorders. This medication has been associated with retinal toxicity in some case reports [3,6-8]. Ocular toxicity can occur in patients with normal renal function and dialysis patients. Typically, patients complain of decreased visual acuity, color blindness (yellow-blue axis), or night blindness. Although these effects are often reversible, some patients experience persistent visual impairment secondary to DFO administration [3].

The mechanism of retinal damage is unknown, but studies have shown pigmentary retinal degeneration [6,7]. Some articles reported optic neuritis and/or macula involvement [9].

Decreased visual acuity and abnormal pigmentation were first recognized in two thalassemic patients [10]. A study on dialysis population treated with DFO showed that 33% of patients have macular changes, that involved peri-macular pigmented deposits, and these findings did not have a significant correlation with the total administered dose or the method of DFO administration [11]. While the incidence of DFO-induced ocular toxicity in patients with normal renal function varies between 0% and 4%, in hemodialysis patients the incidence is higher, affecting 17% to 73% of subjects. Most, but not all, ocular toxicities may resolve.

Risk factors for visual loss in DFO retinopathy includes [3]:

- blood-retinal barrier breakdown associated with diabetes;
- rheumatoid arthritis;
- renal failure; and
- metabolic encephalopathy.

For visual testing, functional testing should include electrophysiology, visual field, and microperimetry. For structural abnormalities, fluorescein angiography and OCT can be used [3].Fundus autofluorescence imaging is a pre-requisite for identifying specific high-risk characteristics. OCT may help detecting extent and location of different retinal changes. DFO retinopathy is always bilateral, but asymmetrical in fundus autofluorescence finding. It may have different patterns [12]:

- minimal change pattern (56%);
- focal pattern (17%);
- patchy pattern (16%); and
- speckled pattern (11%).

There is no association between pattern type and duration of DFO treatment. The area of increased fundus autofluorescence signal indicated diffuse accumulation of autofluorescent fluorophores within a thickened retinal pigment epithelium-Bruch membrane complex or also focal accumulation of autofluorescent outer segment-derived retinoid products in the subretinal space. In early stage of disease, OCT usually shows only focal thickenings or bumps of the retinal pigment epithelium, resembling basal laminar drusen. As the disease progresses, the coalescence of these bumps of pigmented material appears on OCT as thick and hyperreflective dome-shaped lesions that disrupts the architecture of the overlying outer retinal layers. In advanced stages, frank retinal pigment epithelium and photoreceptors atrophy may develop in the macula, as well as migration of hyperreflective subretinal deposits towards the outer plexiform layer interrupting the overlying external limiting membrane [12].

There is no available treatment for patients with DFO retinopathy other than drug discontinuation or dose reduction. In one review article, DFO administration dose has not exceeded 50 mg/kg of body weight in patient with iron overload [3].

In our case, despite the fact that the dose of DFO did not exceed 50 mg/kg, vision problems occurred. She was alert and could explain her complaint well. But in elderly or bed-ridden status patients, vision problem may go undetected. In ESRD patients, frequent blood transfusions and iron therapy (per os and i.v.) are performed. Therefore, it

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is necessary to monitor the patient vision condition, after the injection of DFO. If vision disorders are not noticed early, a permanent damage of retina may occur, as long as permanent vision loss.

In addition, before starting iron chelation therapy, clinicians should consider other markers of iron overload together with ferritin (liver iron concentration, transferrin saturation, deferoxamine test) in order to minimize the toxic side effects due to iron chelators.

**CONCLUSION**

In conclusion, deferoxamine is the most important drug for the treatment of hemosiderosis secondary to long-term treatment with frequent blood transfusions or long-term iron therapy. However, sight-threatening retinopathy may occur after DFO therapy. There is no gold standard identification of ocular toxicity in DFO therapy. Among the patients at highest risk, there are those affected by diabetes, renal failure, rheumatoid arthritis, and metabolic encephalopathy. In renal failure patients under regular hemodialysis or peritoneal dialysis, iron overload can occur due to iron therapy and frequent blood transfusions. Aluminum intoxication can also be effectively treated with DFO. Most dialysis patients suffer from asthenia, weakness, diabetic, and other elderly-related disorders, among which poor vision.

Clinicians need to keep in mind the possible adverse effects of DFO therapy, in order to avoid permanent visual loss.

**Key Points**

- Visual problem is not uncommon in ESRD patients
- Iron overload is also common in ESRD patient due to iron supplement and frequent blood transfusion for chronic anemia
- Early detection and daily assessment of vision problems after DFO are needed to prevent permanent damages to the retina
- After discontinuing the medication, visual problems will resolve gradually
- Afterwards, follow-up with OCT visits should be performed for at least one year
- Fundus autofluorescence imaging is a pre-requisite for identifying specific high-risk characteristics. OCT may have clinical usefulness in detecting extent and location of different retinal changes

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**Conflicts of Interest**

The author declares he has not competing financial interests concerning the topics of this article.

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