Review

Ocular Siderosis

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Abstract:

Ocular siderosis refers to intraocular iron deposition in ocular tissues caused by the long-time retention of penetrating iron-containing foreign bodies, commonly leading to a series of characteristic alterations and severe disorder of visual function. Ocular siderosis, rarely seen in the clinic, can cause irreversible retinal injuries and visual function damage and can even affect the appearance of the eyeballs. These effects significantly decrease the quality of life of patients and lead to poor prognosis. This study summarizes ocular siderosis with respect to pathogenesis, clinical manifestations, diagnosis, treatment, and sequelae, with the aim of assisting clinicians in the diagnosis and treatment of ocular siderosis. (***Eye Science 2013; 28:108-112***)

Keywords: ocular trauma; ocular foreign bodies; ocular siderosis

Ocular trauma is one of the most commonly encountered eye issues with outcomes that range from decreased visual acuity to blindness and even enucleation. The incidence of ocular trauma has clearly increased along with global industrialization. Across the world, approximately 1.6 million cases of bilateral blindness, 2.3 million of bilateral poor visual acuity, and 19 million of unilateral poor visual acuity or unilateral blindness have been caused by ocular trauma[1]. Statistical data show that inpatients with ocular trauma accounted for around 1/5 of all inpatients in 30 hospitals in China over the past decade. Chunxia Jin et al[2]. found that the main causes of ocular trauma included contusive injuries (51.72%), penetrating injuries(26.03%), chemical burns (10.13%), thermal burns (4.52%), explosive injuries (3.40%), and orbital injuries (0.06%). In cases of open ocular trauma, the incidence of the retention of intraocular foreign bodies was 28.6%[3], with metal foreign bodies, and especially iron-containing foreign bodies, accounting for 78% to 86%[4,5]. When penetrating ocular injuries occur, iron-containing foreign bodies penetrate into ocular tissues and are retained within the eyes (with durations ranging from several days and months). This causes iron deposition in the ocular tissues, which presents as yellow-brown particles around the ocular lesions[7]. Previous studies[6] reported that the youngest subject diagnosed with ocular siderosis induced by the retention of iron-containing intraocular foreign body was aged 18 days and the oldest was aged 8.

Pathogenesis

Bunge et al[8]. explored the underlying pathogenesis of ocular siderosis and found that iron reacts with carbon dioxide to form ferrous carbonate, which steadily infiltrates and diffuses into surrounding tissues. There, it finally forms iron oxide, binds with proteins, and then forms a type of iron-protein compound consisting of yellow-brown deposition particles. Excess amounts of iron ions cause a series of cellular enzyme reactions, and iron-induced lipid peroxide possibly leads to retinal degeneration.

Iron ion has a high affinity for ectoderm-derived tissues. Therefore, iron ion is frequently seen in the lens epithelia, sphincter and dilator pupillae, ciliary epithelia, retinal inner and outer nuclear layers, retinal ganglion cell layer, and pigment epithelial layer. Iron ion is also detected in the corneal stromal and endothelial cells, anterior surface layer of the iris, iris stromal, vascular space, and occasionally in the trabecular meshwork of the anterior chamber angle and surrounding phagocytes. The incidence time and

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rate of iron deposition vary considerably in clinical practice[8].

Pathologic and clinical manifestations

Iron-containing foreign bodies mainly cause cellu lar injuries. Iron deposition at different sites, especially the lens and retina, can lead to a variety of severe clinical and pathologic manifestations as follows:

1. Cornea: iron deposition is mainly seen as brown particles in the corneal stroma, especially the peripheral corneal stroma, and leads to probably development of bullous keratopathy, corneal stromal edema, and angiogenesis.

2. Anterior chamber angle: iron deposition is detected in the pectinate ligaments of the chamber angle, trabecular meshwork and surrounding phagocytes. However, histological studies show no sign of chamber angle blockage by iron deposition. Previous studies indicated that the retention of iron-containing foreign bodies for approximately 15 weeks caused damage to the trabecular meshwork. Iron ion was discharged via the trabecular meshwork and deposited within the trabecular meshwork, which induced trabecular meshwork degeneration and blocked the flow of aqueous humor, leading to secondary glaucoma.

3. Iris: most iron deposition was noted on the anterior surface layer of the iris, followed by the iris stroma, sphincter, and dilator pupillae. Several months after onset of disease, the iris appeared blue-violet, mild pupil dilation was observed, and the pupillary response and reflex to light became sluggish or even disappeared; this could not be treated by miotic therapy. Some scholars reported that patients with ocular siderosis experienced a series of pupillary alterations before visual acuity declined: symptoms were initially pupillary dilation and sluggish light reflex and response, followed by heterochromic iris and iris atrophy. Therefore, pupillary alterations serve as a sensitive index of ocular siderosis.

4. Ciliary body: iron deposition was mainly seen in the epithelial cells of the ciliary body, but seldom in the ciliary muscle. Iron deposition may cause ciliary body degeneration, atrophy, and decreased secretion of aqueous humor while retaining a larger amount of proteins. Several years later, open angle glaucoma might be induced and intraocular pressure gradually elevated. This special type of glaucoma has been named "subclinical iron deposition-induced secondary glaucoma." When patients with linear residual corneal scars accompanied by iris holes present with unilateral intraocular pressure elevation, subclinical iron deposition secondary glaucoma should be primarily considered even if no manifestations of iron deposition are observed. Previous reports of gonioscopy examinations revealed no signs of anterior synechia, angle recession, or angiogenesis, *etc.*, but brown pigment was accumulated in the trabecular meshwork. All these outcomes confirm the diagnosis of subclinical iron deposition secondary glaucoma.

5. Lens: initially, iron deposition is seen as evenly distributed brown particles in the epithelial cells beneath anterior lens capsule, and then noted as diversely distributed brown iron spots due to the proliferation of lens epithelial cells. Iron particles show a ring shape or brown floral hoop arrangement when mydriasis is given. Meanwhile, the cortex is seen as diffusive yellow opacity, which is a typical clinical manifestation of iron deposition. Lens opacity intensifies and is followed by lens atrophy, iridodonesis, or lens dislocation, *etc*. The incidence of cataract serves as a sensitive clinical manifestation of early iron deposition. Virata conducted animal studies and found that cataract occurred after a 4-week retention of iron-containing foreign bodies in rabbit eyes. Compared with iron foreign bodies in the vitreous cavity, foreign bodies in the lens are less likely to give rise to retinal damage. In general, the subjects with iron foreign bodies in the lens had desirable prognoses while those with foreign bodies in posterior segment had poor prognoses, probably associated with the difficulty of iron ion diffusion and whether iron ion had reached the retina.

6. Vitreous: the concentration of iron ion within both the aqueous humor and vitreous was enhanced after the penetration of foreign bodies. Since constant circulation of aqueous humor discharged partial iron ion, the elevation of iron ion concentration was less in the aqueous humor than in the vitreous[10]. During the early stage of retinal injury, a substantial quantity of the iron ion was neither dissociated nor entered photoreceptor cells. The measurement of iron ion

concentration in the aqueous humor and vitreous assisted in differentiating the nature of foreign bodies and understanding the dissociation of iron ion. Based upon these outcomes, the optimal time of surgery could be determined that was beneficial to postoperative recovery.

Iron-containing foreign bodies within the vitreous are likely to result in damage to the ocular structure and function. Besides mechanical injuries and inflammatory reactions, decomposition products of iron may induce delayed chemical reactions, leading to retinopathy. Iron oxide destroys the hyaluronic acid in the vitreous and causes irreversible vitreous liquefaction and opacity by dissociation. Clinically, a variety of signs may be observed including brown iron deposition, vitreous degeneration and liquefaction, relatively evident grey-white tiny opaque particles, or asteroids, lamellae, and strip opacities. Patients with intravitreous foreign bodies, regardless of retention time, may present with clinical manifestations of iron deposition of various degrees in the posterior segment, secondary glaucoma, and poor prognosis.

7.Retina: the retina is extremely sensitive to iron toxicity, which provokes retinal detachment, pigment epithelial atrophy, and arteriole stenosis. Dispersive brown iron deposition was seen on retinal surface followed by retinal degeneration and atrophy over disease progression. Patients presented with night blindness and visual field constriction[11]. Such symptoms probably resulted from the Haber-Weiss reaction, in which highly reactive hydroxyl radical (HO) is generated from an interaction between superoxide (O_2^-) and hydrogen peroxide (H_2O_2), stimulated by iron ion. Iron deposition was initially observed in ganglion cells, provoking cellular swelling, degeneration, atrophy, and "disappearance." Subsequently, full-thickness retinal defects, photoreceptor cell degeneration, neuroglial cell proliferation, pigment epithelial proliferation, migration of pigment surrounding retinal vessels may occur. In addition, retinal glial cell proliferation and subretinal leakage may lead to exudative retinal detachment. A fundus angiogram revealed that ischemia initially emerged surrounding foreign bodies and gradually diffused[12]. Previous studies[13] reported that long time retention of iron-containing foreign bodies caused retinal pigment epithelial defects and cystoid macular edema. Yinong Yan[14] used light and electron microscopy to observe the retinal changes of 25 rabbit eyes at for 1 to 30 days after the penetration of iron-containing foreign bodies and found that topical retinal degeneration and necrosis occurred at 2 days. The necrotic tissues were replaced by retinal pigment epithelia and glial cells, resulting in severe retinal atrophy at 7 to 30 days.

8. Choroid: during early stages, the choroid was not affected. In late stages, retinal atrophy was seen, followed by chorioretinal adhesion.

Diagnosis

1. History of disease: most patients show a definite history of ocular trauma. Initially, no discomfort was induced shortly after the penetration of iron-containing foreign bodies, while decreased visual acuity and elevated intraocular pressure steadily occurred due to the diffusion and deposition of iron[15]. 2. Clinical manifestations: typical clinical symptoms and physical signs included decreased visual acuity, eye hyperemia, heterochromic iris, mild pupil dilation, lens opacity, and brown pinpoint or flower-hoop shaped iron particles beneath the anterior lens capsule in the peripheral pupil. 3. Auxiliary examination: imaging tools including ocular B-ultrasound and orbital CT scan are mainly used for detection and diagnosis of intraocular metal foreign bodies based on the patients' clinical information[16]. Multispiral CT could detect 100% of intraocular metal foreign bodies as high signal intensity accompanied by artifacts and partially display non-metal foreign bodies[18,19]. CT is not accurate for detecting tiny foreign bodies[20], depending on slice thickness, density and size of foreign bodies and intraocular position. CT scan is unable to detect foreign bodies with a diameter<1 mm at a slice thickness of 2 to 5 mm[21]. B-ultrasound is capable of precisely differentiating intraocular from extraocular foreign bodies. Dynamic examination is beneficial for the diagnosis of foreign bodies in the orbit. Intraocular foreign bodies are mainly located in non-echo region of the vitreous and lens; therefore, B-ultrasound reveals intraocular foreign bodies as high signal intensity accompanied by comet-tail artifacts and echo. If foreign bodies

were located in eyeball wall, it was difficult to differentiate deep sclera from eyeball wall. This problem could be resolved by reducing the sensitivity of instruments, minimizing the echo of the eyeball wall, and highlighting the echo of foreign bodies. X-ray, which is highly accurate in diagnosing intraocular metal foreign bodies, has been widely applied in most basic-level hospitals[22]. ERG is another sensitive tool in the early diagnosis of iron deposition and clinical evaluation on its progression. In early stages, photoreceptor cells showed microstructural lesions that were mild, topical, and slowly progressing. ERG changes emerged prior to apparent injuries. In patients complicated with cataract, ERG is probably the unique tool to detect retinal changes. Previous clinical and animal experiments confirmed that ERG recovery was obtained after timely surgical removal of intraocular foreign bodies[23]. Early mild ERG damage showed reversible increases in a-wave or b-wave amplitude and normal ocular manifestations. The amplitude of a-wave or b-wave decreased or even disappeared by supplementing with a small dosage of iron. However, permanent damage might be induced in later stages. As a result of gravity action, foreign bodies in the posterior segment are likely to deposit beneath the vitreous, which should be the target of clinical diagnosis in suspected patients[24].

The reasons for misled or missed diagnosis of iron deposition included: subjects with no definite history of ocular trauma, those presenting with severe decreases in visual acuity at diagnosis, those mistakenly diagnosed with corneal perforation and receiving no further examinations, those misdiagnosed by X-ray, those misdiagnosed with uveitis, complicated cataract and glaucoma, *etc.*[41].

Clinical treatment and sequelae

The treatment and management of iron deposition are still debatable. The optimal time of operation and the prognosis of retention and removal of foreign bodies are elusive. Surgical treatment is a primary option, but the incidence of iron deposition cannot be prevented even after the removal of foreign bodies due to iron dissociation. Thus, medicinal therapy is of extraordinary value in the clinic. The choice of surgery is determined by the position of the foreign body and the incidence of complications. Prognosis is associated with the size, position, chemical composition, the presence of encapsulated foreign bodies, and the retention time of the foreign bodies, *etc.*[24]. Asencio-Duran M et al[25]. reported one case of a 3-year retention of foreign bodies that underwent phacoemulsification and IOP implantation combined with vitrectomy and showed an increase in visual acuity from 0.3 to 0.7. Jiting Chen et al[26]. reported that among 10 patients with ocular siderosis undergoing surgery, 2 had postoperative visual acuity recovery from 0.5 to 0.6 and the remaining 8 had no significant improvement in visual acuity. Two cases receiving vitrectomy showed retinal recovery after extraction of silicone oil at 6 and 9 months. Xuexi Li et al[27]. investigated 12 cases with iron deposition in their vitreous cavity, retina or eyeball wall and the foreign bodies were successfully removed by vitrectomy or combined with cataract extraction, endolaser, infusion of silicone oil or expansion gas, etc. Eight patients showed anatomical recovery of retinal detachment. Five had improved visual acuity (41.6%) and 7 had no changes in visual acuity (58.3%). Yikang Dai[15] found that 22 cases with ocular siderosis had improved visual acuity postoperatively, with the maximal elevation from light perception to 0.8 and the minimal increase from light perception to hand motion. The percentage of patients with visual acuity > 0.3 increased from 13.6% to 40.9% postoperatively. Postoperatively, 3 cases with intralenticular foreign bodies had best corrected visual acuity > 0.3, with 0.8 at best. Two of 4 patients (50.0%) with foreign bodies located in eyeball wall had best corrected visual acuity>0.3.Among 15 cases with foreign bodies in the vitreous, only 4 (26.7%) had best corrected visual acuity>0.3. Those with best corrected visual acuity<0.04 all had foreign bodies in their vitreous.

Ocular siderosis should be diagnosed and treated in a timely manner. A missed diagnosis is likely to cause severe consequences. For those subjects with ocular trauma, the physicians should inquire about their history of disease in detail, carefully perform ocular examinations, and emphasize indirect signs. Those with a definite history of impact injuries should receive conventional assisted examination and

undergo surgery early[28].

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