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CASE REPORT

The ophthalmic diagnosis and management of four siblings with Werner syndrome

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Abstract
Introduction Werner syndrome is a rare autosomal recessive disorder caused by mutations in the Werner syndrome WRN gene, on chromosome 8. Those affected manifest early the features of ageing.
Discussion Cataract surgery is prone to post-operative complications in those with Werner syndrome. The development of cystoid macular oedema (CMO) is likely multifactorial. Patients with WS have diabetes mellitus type 2 which can contribute to macular oedema. There is a deposition of abnormal WRN proteins in the macula which also predisposes to macular oedema. The trauma of cataract surgery appears to be the main stimulus for the development of CMO. CMO may, as a result, be difficult to manage in Werner syndrome patients.
Conclusion Further study is needed to elucidate the precise role of retinal WRN protein expression in the development of CMO in those with Werner syndrome. A tailored and more successful approach to the treatment of CMO in such patients may result.

Keywords Werner syndrome · Cataract · Cystoid macular oedema

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Introduction

Werner syndrome (WS) is an autosomal recessive condition characterised by premature ageing. It is also known as progeria of the adult. The incidence of WS is 1:1000,000–1:10,000,000 [1]. Thus, there are only about 1400 people in the world with WS [2]. It is, however, seen in approximately 1:100,000 Japanese individuals in which 75% of diagnoses of WS occur [1, 2].

WS is caused by mutations of the Werner syndrome (WRN) gene at chromosome 8p12 [3]. More than 30 WRN mutations have been identified in patients with WS [4]. The genetic defect affects the transcription of the WRN protein which is essential for replication, repair, recombination, and transcription of deoxyribonucleic acid, telomere maintenance and regulation of apoptosis [3, 5].

It is not surprising then that WS is a multisystem condition. The development of those affected by WS is typically normal until the end of their first decade. A growth spurt in adolescence is usually absent and leads to short stature and low body weight. There is often only very limited development of secondary sexual characteristics. Greying and loss of hair, hoarseness and scleroderma-like skin changes occur in the twenties. The development of type 2 diabetes mellitus, osteoporosis and skin ulceration together with cataract formation characterises the subsequent decade [6–8]. Later in life, there is an increased incidence of cardiovascular disease and malignancy to include

thyroid neoplasms, malignant melanoma and soft tissue sarcomas [9].

Many patients with WS thus present initially to endocrinologists, dermatologists or ophthalmologists. Indeed, the condition was first noted by Otto Werner in 1904 who described the presence of cataract in association with scleroderma in four siblings [10].

The prognosis for patients with WS has improved significantly with advances in medicine. Cataract extraction by phacoemulsification is one such advance [11]. The diagnosis and management of patients with WS may still, however, pose significant challenges to ophthalmologists.

Here, we describe four siblings with WS. We highlight their presenting features and the potential for post-cataract surgery complications, in particular cystoid macular oedema (CMO). Other ophthalmic features associated with WS are elaborated.

Case 1

A 34-year-old white, Irish male with bilaterally reduced vision was referred to the ophthalmology service. His Snellen visual acuity was 6/15 bilaterally. He had bilateral nuclear sclerotic cataract. His intraocular pressures and dilated fundal examinations were normal.

This gentleman was of short stature (165 cm) and low body weight (51 kg) (BMI 18.7). He had a high-pitched voice. Tightening of the skin of his face and a 'bird-like' facies suggested scleroderma. Alopecic patches were noted, and there was greying of the hair that remained. The endocrinology team confirmed diagnoses of 2 diabetes mellitus and hypogonadism.

Subsequent genetic testing confirmed a diagnosis of WS.

The patient had uncomplicated right eye cataract surgery (phacoemulsification) with intraocular lens (IOL) implant. The Acrisof IQ SN6CWS Aspheric was used in this surgery and in all surgeries of this case series.

He reported an initial subjective improvement in his vision in the first 2 weeks. However, at his 4-week post-operative visit the visual acuity from his right eye was 6/30. Cystoid macular oedema (CMO) was noted and confirmed with ocular coherence tomography (OCT), a representative image of which is given in Fig. 1a.

The progression of cataract in this gentleman's left eye with an associated reduction in visual acuity to 6/20 necessitated left eye cataract surgery by phacoemulsification 5 months later following which he again developed CMO as is shown in Fig. 1b. Visual acuity from this eye was limited to 6/20.

As there was some non-proliferative diabetic changes noted in the patients, fundi bevacizumab was chosen as the agent of choice for treatment. This gentleman was treated with a total of 13 and 11 bevacizumab injections to the right and left eyes, respectively, unfortunately without improvement in either his visual acuity or OCT appearance.

The injections occurred over a 4-year period, but unfortunately the patient was poor to attend appointments, and in between appointments the patient also developed proliferative diabetic retinopathy with neovascularisation of the optic nerve head and the retina elsewhere bilaterally. This was confirmed with fundus fluorescein angiography (FFA), images from which can be seen in Fig. 2. He had bilateral pan-retinal photocoagulation and subsequently right eye vitrectomy for non-resolving vitreous haemorrhage.

At the time of publication, this gentleman's visual acuity was 6/36 bilaterally. He had persistent macular oedema bilaterally. Figure 2c depicts his left fundus showing pan-retinal photocoagulation, collaterals at the optic nerve head and severe macular ischaemia with peri-foveal collateral vessels.

After this gentleman's diagnosis of WS, his siblings were asked to attend their family doctor for review. Features of WS were documented in three of his eight siblings. Genetic testing confirmed WS.

Case 2

The second sibling with WS, a 30-year-old male, attended the ophthalmology department 2 years after the proband. He too had a low BMI of 18 with a height of 163 cm and a weight of 49 kg. He had noticed blurred vision from his right eye. Like his brother, he also was a type 2 diabetic diagnosed at 25. His visual acuity was 2/60 from the same. He had uneventful right eye cataract surgery by phacoemulsification. One week post-operatively, his visual acuity had improved to 6/20. Unfortunately, he developed CMO and his vision deteriorated to 6/30 at 3 weeks post-operatively (Fig. 3). Cystoid macular oedema resolved post-

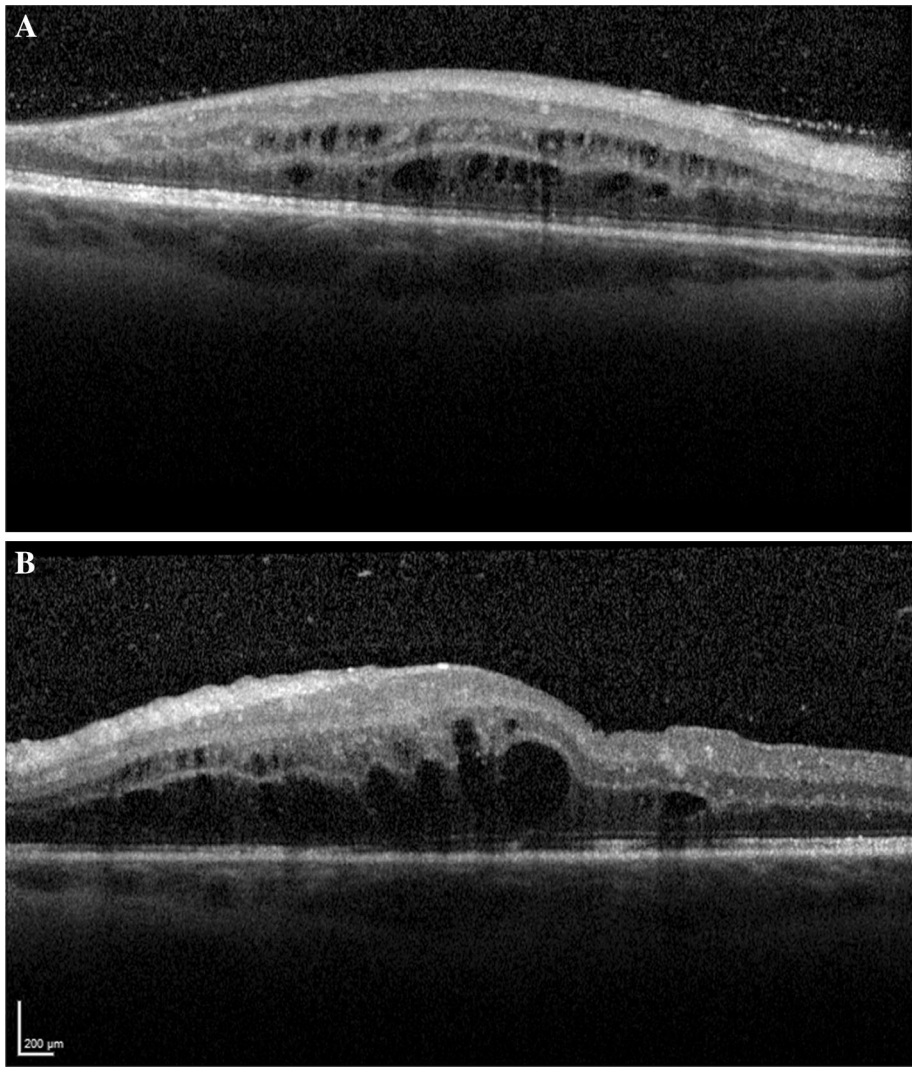

Fig. 1 Ocular coherence tomography images showing right (**a**) and left (**b**) eye cystoid macular oedema in our index patient following cataract surgery

intravitreal triamcinolone injection and subjective benefit to his vision noted.

The following year, left cataract surgery was required as his visual acuity from this eye had deteriorated to 6/30. Post-operatively his visual acuity improved to 6/20, but again he developed CMO. He received intravitreal triamcinolone to his left eye with reduction in CMO and again some benefit to his vision. To date, he has received four and three intravitreal triamcinolone injections to his right and left eye, respectively, for recurring CMO. Currently, he can count fingers with his right eye and sees 2/60 with his left eye.

Case 3

A sister of the proband was referred to the ophthalmology department with blurred vision 2 years after the proband. She was 34 years old. She had visual acuity of 6/7.5 from her right eye and 1/36 from her left eye. She had developed cataract bilaterally. Her intraocular pressures and dilated fundal examinations were normal. She also had type 2 diabetes since her mid-twenties. Like her two brothers, she had a borderline BMI of 19.

This lady had uncomplicated left eye cataract surgery by phacoemulsification with IOL implant.

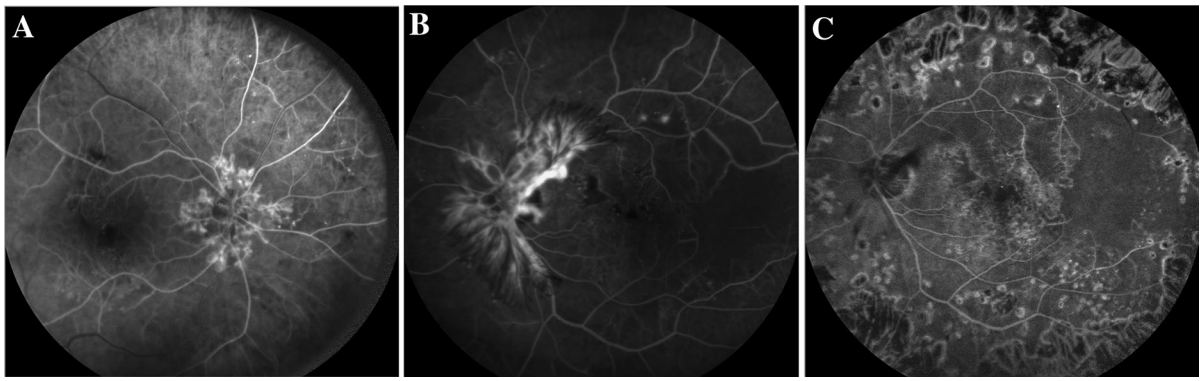

Fig. 2 Fundus fluorescein angiogram images showing proliferative diabetic retinopathy with neovascularisation of the optic nerve head in the right (**a**) and left (**b**) eyes. The left fundus (**c**) has received pan-retinal photocoagulation. Collateral vessels have developed at the optic nerve head. Macular ischaemia associated with the development of peri-foveal collateral vessels is also apparent

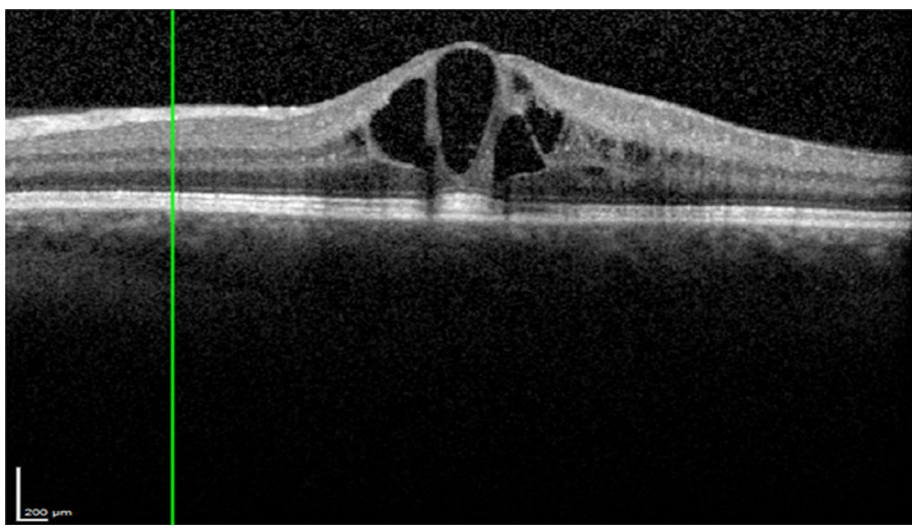

Fig. 3 Ocular coherence tomography in case 2 showing CMO after cataract surgery

The vision in her right eye deteriorated to 6/30 so that 6 months later she had uncomplicated right eye cataract surgery.

One year later she underwent bilateral neodymium-doped yttrium aluminium garnet (Nd:YAG) laser capsulotomy for posterior capsular opacification. At her last review, this patient's visual acuity was 6/6 bilaterally.

Case 4

The fourth sibling with WS, a female, presented with reduced vision in both eyes at the age of 32 years 4 years after the proband. She had a 7-year history of type 2 diabetes mellitus. Like her siblings, her BMI was borderline at 18.6. Visual acuity was 6/9 bilaterally. This lady had uncomplicated left eye cataract surgery followed by similarly uneventful right eye cataract surgery 2 years later. Visual acuity post-operatively was 6/6 bilaterally. She required bilateral Nd:YAG laser capsulotomy for posterior capsular opacification in both eyes at 6 months.

At her most recent follow-up, her visual acuity was 6/6 bilaterally. Her intraocular pressures were 15 and 16 mmHg in her right and left eyes, respectively. Optic disc asymmetry was apparent. No visual field defects were noted at 24/2 Humphrey visual field

testing. This lady is being monitored annually with an intraocular pressure check and visual field testing.

A summary of each patients' case is given in Table 1.

Discussion

Over 100 years following its initial description, patients with WS still pose a challenge to ophthalmologists. This case series highlights the presenting features of WS patients, both ocular—early onset cataract that is bilateral and progresses rapidly and general—elaborated in Table 2 and some potential post-cataract surgery complications (Table 3).

Cataracts are ubiquitous in the WS population. This case series illustrates the need to consider WS in patients who present with bilateral nuclear sclerotic cataracts in their 20s or 30s, particularly, if they are also of short stature with skin changes. Other possible ophthalmic features of WS patients are given in Table 4 [12]. As cataracts in WS tend to progress rapidly to affect vision, and as this syndrome has several important systemic sequelae, e.g. metabolic disorders, cardiac and/or cerebral atherosclerosis and malignancy, early diagnosis prevents both ocular and systemic morbidity [13].

Furthermore, once WS is confirmed, great care must be taken pre-, peri- and post-operatively to minimise the potential complications of cataract surgery. Numerous difficulties following cataract surgery have been previously elaborated and are outlined in Table 5. The majority of such complications were detailed in earlier reports and so, for the most part, followed extracapsular cataract surgery. It has been advocated that WS cataracts can be safely managed with current phacoemulsification [11] and small clear corneal incision surgery techniques, and indeed, the latter two cases described here would support that viewpoint.

The following intraoperative precautions are nonetheless recommended when performing cataract surgery in patients with WS [14]—utilisation of a small incision size of 2.8 mm or less, liberal use of viscoelastic to protect the corneal endothelium, closure of the main corneal wound and side ports using a 10/0 nylon suture to prevent wound dehiscence as impaired wound healing is a feature of WS, and the post-operative use of a relatively weak topical steroid so as not to suppress further fibroblast proliferation which has already been proven by cell culture to occur in WS patients.

Cystoid macular oedema may occur spontaneously [15], following cataract surgery—either extracapsular cataract extraction [14] or cataract extraction by phacoemulsification or after Nd:YAG laser posterior capsulotomy [15] in WS patients.

In one series, three of eighteen eyes with WS that underwent cataract surgery developed post-operative CMO [14]. Kocabora et al. [11] reported a brother and

Table 1 Summary of patient details

Sibling	Sex	Age/years at presentation	Pre-operative VA (R, L)	Post-operative VA (R, L)	Complication(s)	Treatment	VA at last follow-up
1.	M	34	6/15, 6/20	6/30, 6/20	B/L CMO B/L PDR R vitreous haemorrhage	B/L intravitreal bevacizumab Right vitrectomy	6/36, 6/36
2.	M	30	2/60, 6/30	6/20, 6/20	B/L CMO	B/L intravitreal triamcinolone acetonide	CF, 2/60
3.	F	34	6/36, 1/36	6/6, 6/6	B/L PCO	B/L Nd; YAG posterior capsulotomy	6/6, 6/6
4.	F	32	6/9, 6/9	6/6, 6/6	B/L PCO	B/L Nd; YAG posterior capsulotomy	6/6, 6/6

B/L, bilateral; CF, counting fingers vision; CMO, cystoid macular oedema; F, female; L, left eye; M, male; Nd:YAG, neodymium-doped yttrium aluminium garnet laser; PCO, posterior capsular opacification; PDR, proliferative diabetic retinopathy; R, right eye; VA, visual acuity

Table 2 The International Registry of Werner syndrome uses the findings detailed to establish a 'definite', 'probable' or 'possible' diagnosis of Werner syndrome

Cardinal signs
Bilateral cataract
Characteristic dermatological pathology—tight skin, atrophic skin, ulceration, subcutaneous atrophy and characteristic 'bird'-like facies
Short stature
Parental consanguinity or an affected sibling
Premature greying and/or thinning of scalp hair
Further signs
Diabetes mellitus
Hypogonadism—secondary sexual underdevelopment, diminished fertility, testicular or ovarian atrophy
Osteoporosis
Osteosclerosis of distal phalanges of fingers and/or toes. This is an X-ray diagnosis
Soft tissue calcification
Evidence of premature atherosclerosis, e.g. history of myocardial infarction
Mesenchymal neoplasms, rare neoplasms and/or multiple neoplasms
Voice changes high-pitched, squeaky or hoarse voice
Flat feet
Definite All cardinal signs and two further signs
Probable The first three cardinal signs and any two others
Possible Bilateral cataracts or dermatological alterations and any four others
Exclusion Onset of signs and symptoms before adolescence

Our index patient had all the cardinal signs of Werner syndrome and three others (diabetes mellitus, hypogonadism and a high-pitched voice), thus satisfying the criteria for a definite diagnosis

Table 3 General features of Werner syndrome

Short stature
Low body weight
Thin extremities
Senile appearance
Thinning and greying of hair on scalp and beard area
Scleroderma-like skin changes skin wrinkling
Bird-like face
Beaked nose
Skin ulceration
Soft tissue calcification
Skin cancers
Nail dystrophy
High-pitched squeaky or hoarse voice
Dyslipidaemia
Osteoporosis
Bone deformities, e.g. hallux valgus
Atherosclerosis

Table 4 Ophthalmic features of Werner syndrome [1]

Cataract
Nystagmus
Blue sclera
Proptosis,
Keratoconjunctivitis
Cloudy corneas
Iris telangiectasia
Retinitis pigmentosa
Macular degeneration
Chorioretinitis
Glaucoma

sister with WS who each underwent bilateral cataract surgery. One of the four eyes developed post-operative CMO. Here, four of eight eyes developed CMO after cataract surgery.

In any case, the exact pathophysiology of CMO in WS remains unclear. Irvine Gass syndrome may explain some, e.g. those responding rapidly and completely to topical indomethacin [11], not all cases,

Table 5 Potential post-cataract surgery complications in patients with Werner syndrome

Wound dehiscence [2]
Peripheral anterior synechiae [2]
Corneal endothelial decompensation [3] which may necessitate corneal transplantation [4]
Unplanned filtering bleb [2, 5] and cystoid macular oedema [2, 6, 7]
Epiretinal membrane formation [2]
Anterior ischaemic optic neuropathy [2]

e.g. those that occur spontaneously [15], of CMO in WS patients. These patients frequently have type 2 diabetes mellitus which predisposes them to developing macular oedema, particularly following cataract surgery. Indeed, diabetic control in all four of the siblings described here was sub-optimal. Vitreous traction is an unlikely explanation for CMO in WS patients. Neither in the cases described here nor in another reported case [15] did vitrectomy see improvement or resolution of CMO. Inflammation is similarly an unlikely explanation for CMO in WS patients as evidenced by the poor response to both intravitreal triamcinolone and bevacizumab both in the cases described here and elsewhere [15].

Immuno-histochemical analysis of WRN protein expression in human retinas showed that WRN proteins are expressed in the cytosol of Müller cells of the inner and outer nuclear layers [15]. Indeed, WRN proteins are expressed in 'normal' retinas from elderly people. Previous studies have indicated that pathological changes such as swelling and death of Müller cells were closely related to the onset of CMO [16, 17]. It has also been suggested that the pathological changes of dominantly inherited CMO affected mainly Müller cells [17]. The expression of WRN proteins in Muller cells of adult human retinas indicates that WRN gene is active in Müller cells and so a pathophysiological link may exist between the mutation in the WRN gene and the development of CME in patients with WS [15]. Put another way, the absence of WRN protein expression in Müller cells in patients with WS may cause the development of CME associated with Müller cell dysfunction [15]. Further studies are needed to demonstrate the precise role of WRN protein expression in Müller cells and its association with the development of CMO [15].

It is unclear why the female patients did better than the male patients in this case series. Due to frequent missed clinic both ophthalmology and endocrinology, it is unclear whether the patients' diabetic control played a role. There are no HbA1c results available for the patients at the time of surgery. Subsequent HbA1c measurements for all four patients have been consistently raised. In a literature review, there was no articles found comparing CMO based on gender.

The failure to respond to several treatment types and the poor visual outcome in both siblings who developed post-operative CMO described here highlights the difficulty in treating WS patients who develop this problem.

It has been postulated that there may be an increased incidence of normal tension glaucoma and primary open-angle glaucoma amongst those with WS(19). One of the siblings in our case series is currently being monitored for normal tension glaucoma. As type 2 diabetes is more prevalent in WS patients than the general population and as it starts at a younger age, it stands to reason that there is an increased incidence of both diabetic maculopathy and retinopathy in WS patients.

Conclusion

WS is an unusual and uncommon cause of bilateral cataract in young people. Early recognition of the syndrome, however, can reduce ocular and general morbidity. Cautious cataract surgery by phacoemulsification is often successful. Post-operatively visual acuity may be limited by the development of cystoid macular oedema, the exact aetiology of which is uncertain, but which is frequently resistant to multiple treatment modalities. Further study is needed to elucidate the precise role of retinal WRN protein expression in the development of cystoid macular oedema in those with WS [15]. A tailored and more successful approach to the treatment of cystoid macular oedema in such patients may result.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent Informed consent was obtained from all individual participants included in the study.

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